Endocrinology

The Bulletin *of the*
Association *for the* Study *of*

Internal Secretions

March-April, 1926

THE NEUROLOGICAL AND ENDOCRINOLOGICAL ASPECTS OF ICHTHYOSIS, CHRONIC INDURATIVE ECZEMA AND SOME OF THE MINOR FORMS OF SO-CALLED TROPHIC CHANGES IN DERMAL TISSUES*

F. M. POTTENGER, M. D.
MONROVIA, CALIFORNIA

INNERVATION OF THE DERMAL TISSUES

The skin and its appendages, including the nails, hair and pigment bodies, the pilomotor muscles, and the sweat glands; likewise the subcutaneous tissue and bones, are subject to many changes effected through the vegetative nerves. The subcutaneous tissue and bones belong to what has been termed by some writers the "passive" tissues because of their peculiar lack of secretory and motor function.

The skin and its appendages is supplied by both the sympathetic and the parasympathetic components of the vegetative system. There is sympathetic innervation to all these structures. The parasympathetic innervation, however, is more limited and indefinite except in case of a few body areas.

* Read before the Tenth Annual Scientific Meeting of The Association for the Study of Internal Secretions, Dalls, Texas, April 20, 1926.

The preganglionic fibers which pass upward to the cervical sympathetic ganglia carry impulses for vasoconstriction, pilomotor action, sweat secretion, pigment control and the nutrition of the hair of the face and head; also trophic control for the subcutaneous tissue and the bones of the face and head. This is evident from the changes produced by removal of the cervical ganglia. The vasodilator fibers and fibers for sweat inhibition for the face and head come from cranial parasympathetics. As far as known pilomotor action for the face and head depends entirely upon the sympathetics. For the remaining portions of the body, with the exception of the genitalia, vasoconstriction, as well as vasodilatation, pilomotor action and sweat secretion—both activation and inhibition—are due to the sympathetic nerves alone. For the external genitalia the vasodilator fibers and the sweat inhibiting fibers course in the sacral nerve of the parasympathetics.

Vasomotor, pilomotor and sweat reactions are all independent of each other; so we must recognize different systems of neurons presiding over each of these functions.

Aside from the sensory impulses which may be picked up from the skin and its appendages to produce reflex action in dermal structures we have impulses which arise in the internal viscera and also in the higher centers of the brain. These structures are particularly influenced by such emotional stimuli as fear, pain, anger and shame.

Not only are the dermal structures under the influence of the vegetative nerves but they are also subject to the influence of various products of the glands of internal secretion, such as that of the thyroid, pituitary, adrenals and gonads. They also are the possessors of automaticity in action, by which we mean action on the part of the cells themselves without the intervention of nerves or other outside stimuli. Without outside stimuli internal respiration may be carried on and the cells are able to protect themselves from injurious substances which tend to enter through their limiting membranes, and they are able to get rid of substances of a harmful nature which are formed within the cells themselves. Through the nerves and internal secretions, however, their action is integrated and correlated with other structure of the body. There is a very close relationship between the skin and its appendages and certain endocrine se-

cretions. Particularly is this shown in the pigment changes in adrenal insufficiency and at times in pituitary disorders; and more commonly in the changes in the skin and subcutaneous tissue, and the hair in myxedema, and in hypothyroid states of a lesser severity.

COMMON PATHOLOGICAL CONDITIONS AFFECTING THE DERMAL STRUCTURES

Dermal structures are subject to many pathologic changes of both hyper- and hypo-active types. Such are vasomotor disturbances; atrophy and hypertrophy of the skin and subcutaneous tissues; dryness, scaliness, induration and fissures of the skin; dryness, early grayness and loss of hair; changes in the nails, and hyper- and an-hydrosis. Hypertrophy and rarefaction of the bones also occur at times. Although the bones do not belong to the dermal structures they are influenced by and through the same vegetative systems.

The explanation of such clinical manifestations is often found in the domain of pathologic changes in the physiologic mechanism of the vegetative nervous system and hyper- or hypofunction of the glands of internal secretion. Many of these pathologic manifestations are of a trophic nature, which fact brings up the question of whether or not there are nerves whose sole function is trophic. Many writers have been satisfied to believe that all trophic changes in these structures can be explained on the ground of changes in the vasomotor nerves, but the argument is raised against this that anemia of the skin, no matter how marked, does not produce atrophy. Anatomy and physiology so far offer no answer to this question, but clinical observation seems to suggest that trophic nerves are a possibility. It is quite probable, however, that trophic changes in these structures may be produced by action directly upon the cells without the intervention of nerves and without changes in glandular secretion, such as that of the thyroid.

In my experience in the treatment of tuberculosis, I have been much interested in the condition of the skin and its appendages. The skin is often dry and scaly, and the hair dry and brittle, with a tendency to fall out and to become prematurely gray. Sometimes pigment changes are present and local atro-

phies are very common. There are also pilomotor manifestations, changes in sweat secretion and alteration in the nails.

Such conditions have usually been ascribed to the fever; but this does not explain. They may be classed, physiologically, as disturbances in the various mechanisms of the skin and its appendages—vasomotor, pilomotor, sweat and trophic; consequently they are representative of an altered function in the vegetative systems which control these structures. Especially are some of these changes found in hypofunction of the thyroid gland. Whether the changes met in tuberculosis are due to hypofunction of the thyroid; or partly this and partly to a disturbance in the vegetative nerves, particularly the sympathetics, and changes in the cells themselves, we are not able to say, for all of these systems show evidence of injury during the course of a long-drawn-out clinical disease accompanied by toxemia. This is not peculiar to tuberculosis, but is found in many states of chronic toxemia and also in states of malnutrition.

This clinical picture, so often met in tuberculosis, led me to become interested in more serious manifestations in the dermal structures. It seemed reasonable that the same underlying pathologic physiology might be present in other dermal affections of a trophic nature, such as ichthyosis and chronic eczema.

Ichthyosis. Ichthyosis is described as a hypercornification, the skin being susceptible to irritation, eczema and kindred conditions. In patients suffering from ichthyosis the hair of the scalp and brows is usually dry and lusterless. The skin as a rule loses its elasticity, so that at times fissures develop. The subaceous and coil glands of the skin usually show a deficiency in secretion. The skin is dry, scaly, inelastic and thickened.

Ichthyosis usually appears soon after birth, although in some instances it develops later in life. There seems to be a definite hereditary tendency. It has been suggested that the condition was probably due to toxins, and yet there has been no real definite toxin suggested. More recently it has been considered as due to a hypothyroid state, or a disease of the nerves, yet all of these suggestions have been characterized by indefiniteness.

That these dermal manifestations depend upon inherent characteristics of the individual is apparent when it is noted that they usually develop at or soon after birth, and that often

there is a familial relationship as shown in Cases 3 and 5 herein reported.

An interesting and suggestive characteristic of ichthyosis is that it changes with weather. It is usually milder in the summer and more severe during the colder season; in fact, patients suffering from ichthyosis usually stand cold poorly. Sometimes the milder cases entirely disappear during the summer time. This has been ascribed to the fact that the patient perspires in the summer, which moistens the skin and causes it to assume a normal condition; but this increased sweating is more probably simply another evidence of an improvement in the physiological control of these structures in summer.

Chronic Eczema is a dermal infection, recurrent in nature, in which there is marked irritability of the skin with itching and induration, and in which the skin sometimes shows marked folding and creasing. There seems to be a hereditary factor in its etiology.

In attempting to assign a cause to such pathological conditions as ichthyosis and the chronic form of eczema, likewise the minor dermal changes herein described as noted in chronic tuberculosis, the relationship to the vegetative nervous system at once forces itself to the fore, because all functions of these structures which are affected are presided over by vegetative nerves. The relationship to weather conditions suggests very definitely the relationship of the disease to those factors which control metabolism, because the disease is worse in cold weather when greater metabolic activity is acquired.

Increased energy requirements in winter is met by increased activity of all those mechanisms which increase energy: the sympathetic nerves become more sensitive and the energizing glands of internal secretion, particularly the thyroid, more active.

It has been pointed out by Kendall that more thyroid secretion is circulating in the tissues in the winter and thus meets the extra energy requirements of the cold. In case of a deficiency in secretion it can be readily understood how this increased demand fails to be met, how metabolism lags and how the patient is unable to supply the extra amounts necessary for maintaining normal conditions in the tissues. As a result the

skin becomes dry, scaly and lusterless, and the patient endures cold badly.

REPORT OF CASES

The following cases will illustrate some of the points made in this paper, particularly as regards suggestions of etiology.

Case I. K. O., Japanese, aged 17, entered the Pottenger Sanatorium February 6, 1922, suffering from acute caseous tuberculosis, involving both upper lobes, with high fever. He also had a marked ichthyosis which had appeared soon after birth, the skin being dry, thickened and scaly. It resembled the scales of a fish. Large and small scales were continuously thrown off. The patient always suffered from cold.

In spite of active tuberculosis he was put on thyroid, beginning with 1 gr. and increasing to 2 gr. daily. Calcium chloride, 10 cc. of 5% solution, was given once a week from July 16 to October 5, 1925. The patient improved very greatly. The large scales disappeared. The skin did not become entirely smooth but smoother than it had ever been and also somewhat moist. The tuberculosis also improved greatly. The patient formed a small cavity in the right lung and a large cavity in the left. He became fever-free and gained considerably in weight.

Case II. F. M. G., aged 68, was suffering from far advanced tuberculosis with cavities in lung, high temperature, also tuberculosis of the larynx with ulceration. He had very marked ichthyosis which had existed from birth. The skin was dry, scaly and was continuously thrown off in large scales. This condition existed over the entire body. He suffered from cold and always wore woolen union suits, even in summer.

He was put on treatment while in the sanitarium—four and one-half months. Thyroid was given, 2 gr. daily, beginning after the patient had been in the sanatorium two weeks. This was continued during his stay except during a two-weeks period when he was having a severe attack of singultus. At the same time he was given calcium chloride, 10 cc. of 5% solution, every four days. He improved very greatly. The scales almost entirely disappeared from the body; the skin became quite smooth and somewhat moist, and the patient declared that it was the first time he had had any relief during his life.

Case III. J. R., aged 28, had dry scaly skin since birth, being worse in winter than in summer. Face and hands chapped easily during cold weather. There was no itching. On exposure to the sun the skin burned and blistered easily but did not tan.

Family History. The father's height was 6 feet; weight, 210 pounds; his skin was soft. The mother was 5 feet 10 inches in height, and weighed 220 pounds. Her osseous system was well developed. Her skin had a tendency to dryness. One brother died of pneumonia; one died from accident at 3½ years. One brother, aged 15, has dry scaly skin; one brother, aged 21, has scaly skin on exposed surfaces; one brother, aged 27; one sister, aged 25, and one sister, aged 9, all have a slight tendency to dryness.

Physical examination of the patient showed skin uniformly dry and scaly over the entire body, with some small indurated folds on flexor surface of the arms. Scales in the nature of thin white flakes show both on exposed and unexposed surfaces. The hair was coarse but not unduly dry, and the scalp scaly.

The patient was suffering from extensive far advanced tuberculosis with cavities and fever.

Medication. Thyroid, 1 gr. daily for two months and 2 gr. daily for six months, together with calcium chloride, 10 cc. of 5% solution every four days during entire period—eight months, were administered. The skin condition improved markedly and at present it is soft and smooth and shows practically no scaling.

Case IV. J. F., aged 24, suffered from asthma up to the age of 17 years. He entered the Pottenger Sanatorium, suffering from moderately active tuberculosis, May 21, 1925. He was discharged February 27, 1926. His skin over both exposed and unexposed parts of body had always been dry and leathery. The eyebrows were scanty. He stood cold badly. On account of the dryness and scaliness of the skin he had always been sensitive.

He was treated by thyroid and calcium chloride; thyroid, 1 gr. daily from June 21, 1925, to August 29, 1925; 2 gr. daily August 29 to December 1, 1925, and 3 gr. daily from December 1, 1925, to date of discharge, February 27, 1926. He is still taking it. Calcium chloride, 10 cc. of 5% solution was given every four days from July 13, 1925, to February 27, 1926.

The skin improved very markedly. The scales disappeared; the skin became soft and moist, and the surface looked about the same as those of ordinary individuals. This was the first relief the patient had had since this condition started as a child.

Case V. Mrs. G. H., aged 26, began having trouble with her skin at the age of 11. This took the form of inflammation with induration and itching, confined to arms and neck. The first attack lasted one year. At the age of 16 she was troubled with the condition from June to December. She had had two x-ray treatments a week in mild doses and improved. At the age of 21 the trouble returned and persisted for some time, beginning with papules which broke, forming pustules and scales. The lesions were very changeable: Sometimes only redness with intense itching; at other times, induration. She scratched lesions in sleep and caused excoriation of the skin. Keeping the arm under the bed covers or protected by clothing increased the symptoms. She always noted that the symptoms were worse when she was nervous and at the menstrual periods. From June to December, 1921, she took 18 x-ray treatments without improvement. These resulted in burns of the skin with telangiectasis. She noticed that the condition was always worse in winter.

I first saw the patient May 1, 1923, at which time the skin over the face and flexor portions of the arms was very thick and thrown into folds. Itching was extremely intense. The skin was dry, scaly and leathery. Excoriations from scratching were present on the arms from the elbow to the wrist. The vessels of the face and arms were dilated as a result of x-ray treatment. She showed scantiness of the external third of the eyebrows and a dry skin over the body; she withstood cold badly, giving the impression of a definite hypothyroidism. She also had a tendency to hay fever.

Family History. Her father was 6 feet tall and weighed 190 pounds. He had a large frame and was always active. There was no early grayness. He died of heart trouble at 53. The mother's height was 5 feet 8½ inches; weight, 182 pounds. She was of large frame but did not appear fat. She had no skin trouble. One brother was 5 feet 5 inches tall and weighed 170 pounds at the age of 42. A sister was 5 feet 5 inches tall and weighed 142 pounds at the age of 39. They had no skin abnormalities. The patient has one child 3 years old who weighs 40½ pounds. She has a slight tendency to dryness of the skin and itching. The condition improved following the use of thyroid. The difficulty returned in cold weather but yielded again to increase in the amount of thyroid.

Menstrual History. The patient was regular until 1925. Since then she has flowed every 18 days. The skin condition was a little worse toward end of the period.

Treatment. Desiccated thyroid was given, 1 gr., daily from May 1 to May 14, 1923; 2 gr. daily from May 14, 1923, to February 4, 1924. This seemed to relieve the condition very satisfactorily until February. From February 4 to March 13, 1924, 3 gr. daily was given. With this dosage the skin cleared and became soft and pliable, but showed signs of recurrence in March, 1924. Four gr. daily was given from March 13 to March 27, 1924, when the patient began to experience slight tremors. Thyroid was then withheld for a short period and then resumed with 3 gr. daily, which amount the patient has taken until the present time. She was also given calcium chloride, 10 cc. of 5% solution, from 2 to 3 intravenous injections a week, from May 1, 1923, to March, 1924. Calcium injections were stopped from March, 1924, to March, 1925. In the spring of 1925 two injections a week were given, and during February and March, 1926, one injection a week was given. Since March, 1923, calcium lactate (20 gr. daily) has been taken by mouth.

As a result of the treatment the skin condition has been markedly improved; the skin has become more moist; the itching decreased and shortly disappeared entirely. The induration has also gradually disappeared, and at the present time the skin shows little evidence of former induration. The thickness which is present is accentuated by the results of the x-ray treatment. Also the excessive nervousness has disappeared. It was noted on September 12, 1923, that the patient had gained 3½ pounds in weight. Hair was then present and normally distributed over the forearms, and the skin had lost much of its leathery appearance. March 26, 1926, except for slight relapses during the winter months each year, the patient has remained in a very satisfactory condition. These relapses quickly disappear under an increased amount of thyroid and the resumption of the intravenous injections of calcium chloride.

DISCUSSION

In the treatment of the above cases ointments and soothing baths, which are usually employed, were purposely omitted. This was an experiment to determine if those measures that are known to influence the neurocellular mechanism presiding over these dermal tissues would produce a favorable response. The manifest difficulties surrounding the treatment of these patients will be evident to all. Part of them were suffering from far-advanced, active tuberculosis. All but one had tuberculosis. Furthermore, the prolonged toxemia had a tendency to cause conditions similar to the ones that we were trying to treat. Foods containing large quantities of calcium should be employed during treatment, and the proteins, which hasten its elimination, should be avoided; but in tuberculous patients such a diet could not be followed. There is no doubt that the improvement in the patient's general condition had some influence in causing the

skin lesions to respond, but that it was not the main factor is made clear by the fact that in all instances the skin affections were present prior to the time the patient had tuberculosis.

I cannot believe that these dermal affections are purely hypothyroid in nature; for, if they were, we would expect a more complete yielding to the administration of thyroid preparations than occurs. In other instances of thyroid deficiency, even cretinism and myxedema, there is a more rapid and more complete response. In case of the patients reported herein, however, the response was not complete in a single instance. We found that thyroid alone would not keep the skin in as good condition as thyroid with calcium added. This was noted even though the thyroid was pushed to the point of causing increased heart action and nervous instability. We also found that while calcium by the mouth, which was given between the series of intravenous injections, was advantageous, it had to be supplemented ever now and then by intravenous administration, especially when relapses occurred. A point indicative of the intimate part played by the nerves is the fact that all of the various mechanisms, trophic, sweat, vasomotor, pilomotor, and even the subcutaneous fat distribution are affected.

The relapses occur during times of nerve stress and when the weather becomes cold. The former are times when nerve imbalance is accentuated; the latter when thyroid deficiency shows most markedly and the calcium content of the cells is relatively low. So it seems justifiable to assume that these lesions do not represent a pathologic condition of one phase of vegetative control to the exclusion of others, but rather a general disturbance in all: the nerves; the endocrine organs, particularly the thyroid; and the automaticity of the cell itself, particularly as it depends upon its ionic content, its permeability and reactivity.

We note that these mild instances of dryness and scaliness of the skin which are met in chronic tuberculosis improve when the patient's nutrition improves and the general physiologic balance is restored. We assume that nerve, endocrine and cell balance are all improved when this condition has been attained. We also at times see the hair become oily and even regain some of its color when health has been regained. The vasomotor and sweat anomalies met in patients suffering from a long-drawn-

out toxemia also disappear with recovery. That these lesions are in part due to the general process of wasting in tuberculosis may be true; but it is desirable to define them more accurately if possible, and this may be done by a careful study of their physiologic control. It is possible that there is a close etiological relationship between these minor changes noted in tuberculosis and the more severe lesions represented by ichthyosis and chronic eczema cited above, even though the former is apparently caused by a disease process while the latter is apparently due to inherited factors.

NON-DIABETIC GLYCOSURIA

HENRY J. JOHN, M. D.
Cleveland Clinic
CLEVELAND

A light or even a heavy glycosuria is not an uncommon finding in the routine examination of patients. In Table I, I have collected references to such findings as have been reported by various observers in the recent literature. Noteworthy among these observations are those in which the condition had been observed over very prolonged periods, viz., from 3 to 35 years.

Various terms have been applied to this non-diabetic type of glycosuria. Thus it has been called diabetes innocens; renal diabetes; renal glycosuria. Such terms as the last two of these are misnomers since glycosuria is always renal, being dependent upon the renal threshold as well as the glycemic level. Glycosuria innocens is a better term since it indicates at least the non-diabetic character of the glycosuria—but for this very reason, since whenever glycosuria is present it is imperative to determine whether or not it is due to a diabetic condition, I have adopted the term *non-diabetic glycosuria* as most applicable to glycosuria of this type.

I shall not review the rather extensive literature on this subject as it is sufficiently covered in the references included in the table. My only object in this report is to add my personal observations to those which have already been reported by others, thus adding further confirmation of the observation that the non-diabetic type of glycosuria has no pathological significance, moreover not only does it require no treatment but no treatment is of any avail. These patients may secrete more or less sugar for many years, without any ill effects. The only important point in these cases is to be sure that the glycosuria is of the non-diabetic type and not due to an early stage of diabetes, for while in the former case no treatment is required, in the second, treatment is vitally essential. It is therefore important to review the necessary steps for the establishment of the correct diagnosis.

A diagnosis should never be based on the presence of glyco-

suria alone, for it is imperative to establish its significance beyond a doubt. Therefore, when the presence of glycosuria is observed, a fasting blood sugar determination and a careful urine examination should be made at once. If the fasting glycemia is above 160 mg. per 100 cc. one may be fairly certain that one is dealing with a case of diabetes. As further confirmation of this supposition, the patient should be instructed to eat a heavy breakfast of pancakes with an abundance of syrup, the blood and urine being examined two and one-half hours

TABLE I
Summary of Observations of Various Authors on Non-Diabetic Glycosuria

Author	Age of Patient at Beginning of Treatment	Sex	Period of Observation	Daily Sugar Output
Parkes, Weber T.	.....	F	35 years	30 gms.
Holst, J. E.	24 years	M	23 years	
Holst, J. E.	7 years	M	22 years	1%
Labbé, M.	6 years	.....	19 years	
Allan, Wm.	17 years	F	18 years	16– 49 gms.
Johnsson, A.	28 years	F	16 years	
Johnsson, A.	.....	F	16 years	
Bailey, C. V.	.....	F	11 years	20 gms.
Garrod, A. E.	8 years	F	11 years	
Labbé, M.	6 years	F	11 years	1.2–0.03%
Johnsson, A.	25 years	M	10 years	
Johnsson, A.	.....	M	10 years	
Garrod, A. E.	12 years	M	9 years	
Paullin, J. E.	16 years	M	7 years	34 gms.
Lemann, I. I.	15 years	M	6 years	Traces
Lewis, D. S.	.....	....	5 years	25 gms.
Lewis, D. S.	.....	....	5 years	16 gms.
Lemann, I. I.	4 mos.	M	3 years	Traces
Faber, K. and Norgaard, A.	26 years	F	3 years	60– 80 gms.
Marsh, P. L.	22 years	F	1.3 years	50– 60 gms.
Marsh, P. L.	.....	....	1.25 years	15–122 gms.
Lemann, I. I.	19 years	M	1 year	Traces
Marsh, P. L.	74 years	M	.....	30– 50 gms.
Goldbloom, A.	20 mos.	M	.....	1%

later; if at that time the blood sugar is normal, even though the fasting blood sugar may have been between 160 and 180 mg. per 100 cc., diabetes can be ruled out, for, if diabetes be present, two and one-half hours after such a heavy carbohydrate breakfast the patient will certainly show a more or less pronounced hyperglycemia. One can go a step further, especially if the data are not clearly defined, and make a glucose tolerance test in the following manner. A sample of fasting blood is taken, after which the patient is given an ice-cold solution of 100 gm. of glucose dissolved in from 250-300 cc. of water, to which the juice of one lemon has been added. Samples of blood

and urine are taken at periods of one-half hour, one hour, and two, three and four hours after the glucose is administered. Even though the fasting blood sugar may be normal, if the patient is diabetic the blood sugar curve will show a slow and prolonged rise with an equally prolonged fall, so that even four hours after the ingestion of the glucose it will not have returned to the normal level. On the other hand, in a non-diabetic individual the blood sugar curve will show a quick rise with an equally abrupt fall, so that in one, or at the most in two, hours after the ingestion of the glucose the curve will return to the normal level. In certain cases the blood sugar content may not show any increase at all, indicating that the individual in question has a very strong tolerance for carbohydrates, that the islands of Langerhans secrete an unusually abundant supply of insulin. By this method, therefore, one can differentiate between the diabetic and the non-diabetic types of glycosuria, and, moreover, in this manner the renal threshold for sugar can be determined, a point which is not only of scientific interest but is also of practical importance for the interpretation of our findings.

However, our observation of the patient with a non-diabetic type of glycosuria should not stop with a single examination, for, as stated above, a true non-diabetic glycosuria remains practically the same as to the sugar content of the urine whatever the diet of the individual—and a series of examinations are needed to determine whether or not this is true in any individual case.

Final conclusions regarding the validity of our belief that non-diabetic glycosuria is truly innocent in character demand prolonged observations of a series of cases, and therefore in Table II, I am submitting my own observations on a group of eight cases for periods of from two to eleven years. In none of these cases was the glycosuria marked, but in all of them the glucose tolerance tests showed a low renal threshold, which accounts for the post-prandial glycosuria. These patients simply "spill" sugar after heavy meals and thus lose small quantities of sugar each day. This loss is of little consequence, however, when we consider that a normal person ingests some 400 gm. of carbohydrates daily in addition to the carbohydrates derived from protein and from fat, so that even if he loses from four to six grams through the urine, this is but a mere

trifle in comparison with the amount of carbohydrates which he utilizes. Moreover, the loss may be disregarded, for it cannot be stopped; there is at present no means whereby the renal threshold may be raised so that the sugar may be retained.

TABLE II

Non-Diabetic Glycosuria
(Author's Series)

	Age When Glycosuria Was Discovered	Sex	Length of Time Cases Have Been Under Observation
I	32 years	M	7 years
II	30 years	M	11 years
III	16 years	M	5 years
IV	46 years	M	10 years
V	44 years	M	2 years
VI	34 years	M	6 years
VII	17 years	F	7 years
VIII	2½ years	M	5 years

A brief review of the histories of the cases reported in Table II may be of interest.

Case I. (109856) A man, 34 years of age. There was no familial history of diabetes. He had been married for ten years and had three children living and well. He had had none of the usual diseases of childhood. He came to the Cleveland Clinic because of his glycosuria, which had been discovered in the course of an examination for life insurance. Because of this finding he had been treated by his family physician for diabetes.

A glucose tolerance test made two years before I first saw him had given the following information:

			Time after ingestion of glucose		
	Fasting		½ hr.	1 hr.	2 hrs.
Bl. Sug. mg./100 cc.	110	75 gm. glucose by mouth	195	200	158
Urine Sugar	0			2+	3+

When I first saw him on January 24, 1922, he had a fasting blood sugar of 128 mg. per 100 cc. and no glycosuria. A glucose tolerance test gave the following results:

			Time after ingestion of glucose				
	Fasting		½ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.
Bl. Sug. mg./100 cc.	128	100 gm. glucose by mouth	207	146	125	107	79
Urine Sugar	0			2+	1+	0	0

Total water intake 850 cc.
Total urine output 850 cc.
Plasma Cl. 655 mg./100 cc.
Bl. Urea 33 mg./100 cc.
Bl. Creatinin 1.8 mg./100 cc.
Bl. Uric Acid 3.5 mg./100 cc.
Bl. N. P. N. 25.2 mg./100 cc.
Bl. Wassermann negative.

These findings made it appear that this was a case of non-diabetic glycosuria. The summary of observations in this case to February, 1924, is as follows:

	1920		1921	1922		1923	1924
Date			Jan. 24	Feb. 14	May 24	Nov. 1	Feb. 11
mg./100 cc.	110		128	104	111	102	80
Urine Sugar	1+	0	1+ 1+	0	1+	1+	0

	1926	
Date	Feb. 17	March 22
Bl. Sug. mg./100 cc...	87	78 (1½ hrs. P. C.)
Urine Sugar	0	3+

Another glucose tolerance test made on February 12, 1924, gave the following results:

			Time after ingestion of glucose				
	Fasting		½ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.
Bl. Sug. mg./100 cc.	85	100 mg.	146	191	117	78	53
Urine Sugar	0	glucose by mouth		3+	3+	tr.	0

Total Water intake 875 cc.
Total urine output 386 cc.
Total sugar intake 100 gm.
Total sugar output 1.54 gm.
Plasma Cl. 585 mg./100 cc.
Bl. Urea 39 mg./100 cc.
Bl. Uric Acid 2.3 mg./100 cc.
Bl. Creatinin 1.1 mg./100 cc.
Bl. N. P. N. 42.6 mg./100 cc.
Bl. Plasma acetone negative.

Case II. (116819) A man 36 years of age. One sister and one brother had diabetes. He had two children, living and well. He had had no illness in childhood or later. He came to the Cleveland Clinic because of glycosuria which had been discovered in 1916 in an examination for life insurance. Because of this finding insurance had been refused. He had had rather frequent urine examinations during the preceding six years, sugar being found repeatedly.

When I first saw this man on September 19, 1922, his urine showed no sugar and his blood sugar 4½ hours after a meal was 114 mg. per 100 cc. A glucose tolerance test on the next day gave the following results:

			Time after ingestion of glucose				
	Fasting		½ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.
Bl. sugar mg./100 cc.	97	100 gm.	113	119	93	63	84
Urine Sugar	neg.	glucose by mouth		tr.	tr.	neg.	neg.

Total water intake 920 cc.
Total water output 960 cc.
Total sugar intake 100 gm.
Total sugar output 0.234 gm.
Plasma Cl. 595 mg./100 cc.
Bl. Urea 15 mg./100 cc.
Bl. Uric Acid 2.3 mg./100 cc.
Bl. Creatinin 1.2 mg./100 cc.
Bl. N. P. N. 21 mg./100 cc.
Plasma acetone negative.
Blood Wassermann negative.

These data showed clearly that we were dealing with a renal type of glycosuria, that is, with a very low renal threshold for sugar, lying somewhere between 119 and 93 mg. per 100 cc. The patient, therefore, would not fail to show glycosuria almost constantly as had been the case during the preceding six years. The data on this case are summarized below.

Date	1916	1917	1918	1919	1920	1921	1922		1924	1925	1926	
							Sept. 19	Sept. 20	April 9	Feb. 2	Jan. 4	Jan. 5
Bl. Sug. mg/100 cc. Fasting....							114*	97‡	110†	89†	92§	
Urine Sugar.....	1+	1+	1+	1+	1+	1+	0	0	0		0	1+

* 4½ hours after eating.
† 4 hours after eating.
§ 2½ hours after eating.

Case III. (122143) A boy 17 years of age. No familial history of diabetes. He had had measles and whooping cough in childhood, chickenpox a year before, a severe attack of mumps at the age of 12. An appendectomy had been performed when he was six years old and a tonsilectomy at the age of seven years. As he had been told he had diabetes he came to the Clinic in March, 1923, giving the following history:

In August, 1922, he had had a bad cold. At that time sugar was found in the urine but he had no clinical symptoms of diabetes. Repeated examinations of the urine occasionally showed sugar but a blood sugar examination had never been made.

When I first saw this patient on March 26, 1923, the urine contained sugar—3 plus—and the fasting blood sugar was 89 mg. per 100 cc. The following day I made a glucose tolerance test with the following results:

			Time after ingestion of glucose				
	Fasting		½ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.
Bl. Sug. mg./100 cc.	84	100 gm. glucose by mouth	113	84	98	79	84
Urine Sugar	0		0	0	0	0	0

Total water intake 975 cc.
Total urine output 363 cc.
Plasma Cl. 575 mg./100 cc.
Bl. Urea 24 mg./100 cc.
Bl. Uric Acid 2.0 mg./100 cc.
Bl. Creatinin 0.91 mg./100 cc.
Bl. N. P. N. 28 mg./100 cc.
Plasma Acetone negative.

No glycosuria occurred during the test, although on the preceding day it had been 3 plus. The tolerance test showed clearly that this boy did not have diabetes. The data in this case may be summarized as follows:

Date	1922	1923 March 26	1923 March 27	1926 Feb. 17
Bl. Sug. mg./100 cc.		89	84	89
Urine Sugar	1+	3+	0	0

Case IV. (106174) A man 50 years of age. No familial history of diabetes. He came to the Clinic because of glycosuria, which had been discovered in 1917 in the course of an examination for life insurance. Repeated examinations of the urine during subsequent years failed to show glycosuria except once, in 1921. On account of this history I made a glucose tolerance test on September 13, 1921, with the following results:

			Time after ingestion of glucose				
	Fasting		½ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.
Bl. Sug. mg./100 cc.	112	100 gm. by mouth	183	180	137	88	64
Urine Sugar	0	glucose		1+	1+	1+	0

Total water intake 900 cc.
Total urine output 1105 cc.
Blood Wassermann negative.

These results definitely demonstrated that we were dealing with a non-diabetic glycosuria in which the renal threshold to sugar lay somewhere between 137 and 88 mg. per 100 cc.

The glycemia-glycosuria history in this case to date may be summarized as follows:

Date	1917	1921	1924				1925			1926 Jan. 5
			Sept. 13	Mar. 16	Sept. 2	Dec. 9	Mar. 20	July 1	Oct. 29	
Bl. Sug. mg/100 cc..			112							56
Urine Sugar.....	1+	1+	0	0	0	0	0	0	0	0

Case V. (137141) A man 44 years of age. No familial history of diabetes. He had had measles, mumps, chickenpox, diphtheria, scarlet fever and whooping cough in childhood, and later in life he had had influenza and amebic dysentery in 1914, while in China. He was married and had four children, living and well. He came to the Clinic because of glycosuria, which had first been discovered six weeks before in the course of an examination for life insurance. In repeated examinations during the following few days the urine sometimes showed sugar and sometimes was sugar free. At that time his fasting blood sugar was 120 mg. per 100 cc. A glucose tolerance test which was made on April 10, 1924, in Baltimore, gave the following results:

			Time after ingestion of glucose		
	Fasting		½ hr.	1 hr.	2 hrs.
Bl. Sug mg./100 cc.	117	100 gm.	216	180	142
Urine Sugar	0	glucose by mouth		1+	1+

Total sugar output 0.845 gm.

This patient came to see me on June 4, 1924, at which time I repeated the glucose tolerance test with the following results:

			Time after ingestion of glucose				
	Fasting		½ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.
Bl. Sug. mg./100 cc.	84	100 gm.	183	163	104	70	59
Urine Sugar	0	glucose by mouth		1+	tr.	0	0

Total water intake 950 cc.
Total urine output 850 cc.
Total sugar intake 100 gm.
Total sugar output 0.17 gm.
Plasma Cl. 585 mg./100 cc.
Bl. Urea 24 mg./100 cc.
Bl. Creatinin 1.1 mg./100 cc.
Plasma Acetone negative.
Blood Wassermann negative.

The above and the following glucose tolerance test, made in California on February 9, 1926, showed that the glycosuria was of non-diabetic origin:

			Time after ingestion of glucose				
	Fasting		½ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.
Bl. Sug. mg./100 cc.	95.2	100 gm.	133.3	150	74	55.5	83.3
Urine Sugar	0	glucose by mouth	0	1+	0	0	0

This is really a case of non-diabetic glycosuria of the spasmodic type with a renal threshold for sugar somewhere between 163 and 104 mg. per 100 cc. This low renal threshold, as stated above, was demonstrated by a glucose tolerance test made in California on February 9, 1926, in reference to which the patient made the following statement: "You may be interested to learn that I have made no attempt to limit my diet in any way. Last week I tipped the scales at 145 pounds and am feeling better than I have felt for years."

The history of this case may in turn be summarized as follows:

	1924		1925		1926
Date	Apr.	Apr. 10	June 4	Mch. 19	Mch. 19	Feb. 9
Bl. Sug. mg./100 cc.		117	84	85	87*	95.2
Urine Sugar	1+	0	0	0	0	0

Case VI. (103131) A man 34 years of age. His father and his father's brother had died of diabetes and one brother had severe diabetes. He had been married 11 years and had two children, living and well. He had had none of the diseases of childhood, but some years before had had a gonorrheal infection. He came to the Clinic because of glycosuria, which had been found in the course of an examination for life insurance. On account of the marked familial history of diabetes, the presence of glycosuria was naturally interpreted as being due to diabetes.

I first saw this patient on May 28, 1921, when his postprandial blood sugar was 110 mg. per 100 cc. As a urine examination on May 31st showed a considerable reduction with Benedict's solution, a glucose tolerance test was performed on June 4th, with the following results:

			Time after ingestion of glucose				
	Fasting		½ hr.	1 hr.	2 hrs.	3 hrs.	4 hrs.
Bl. Sug. mg./100 cc.	111	100 gm.	151	145	77	77	88
Urine Sugar	2+	glucose by mouth		2+	2+	1+	1+

Total water intake 900 cc.
Total urine output 178 cc.
Total sugar intake 100 gm.
Total sugar output 0.206 gm.
Plasma Cl. 490 mg./100 cc.
Blood Urea 14.4 mg./100 cc.
Blood Wassermann negative.

* 2¼ hours after eating.

It was clear that in this case also we were dealing with a non-diabetic type of glycosuria.

The history may be summarized as follows:

	1921			1926	
Date	May	May 28	May 31	June 4	Jan. 9	Jan. 26
Bl. Sug. mg./100 cc.		110		111	88	
Urine Sugar	2+		2+	2+	neg.	neg.

Case VII. (104930) A girl, 18 years of age. No familial history of diabetes. She had not menstruated for 18 months. A tonsilectomy had been performed three years before. She came to the Clinic because of glycosuria, which had not been eliminated even by prolonged dietary restriction.

No clinical symptoms of diabetes accompanied the onset of the glycosuria, which had been first observed in 1920. She had been on practically a starvation diet for two weeks before I saw her, as the result of which her weight had fallen from 123 to 83 pounds, so that she looked like a skeleton and was so weak that she could hardly stand up. Physical examination revealed nothing of significance except the emaciation.

When I first saw this patient on July 27, 1921, glycosuria was present and her blood sugar content was 125 mg. per 100 cc. The following day I made a glucose tolerance test with the following results:

			Time after ingestion of glucose			
	Fasting		½ hr.	1 hr.	2 hrs.	3 hrs.
Bl. Sug. mg./100 cc.	84	100 gm. glucose by mouth	131	141	102	84
Urine Sugar	1+			1+	1+	1+

Total water intake 950 cc.
Total urine output 74 cc.
Total sugar intake 100 gm.
Total sugar output 0.103 gm.
Blood Wassermann negative.
P. S. P. 55/15 (2 hours).
R. B. C.'s 3,590,000.
Hgb. 65%.
W. B. C. 9400.

These data showed clearly that we were dealing with a pure type of non-diabetic glycosuria, this conclusion being confirmed by subsequent observation, for no matter how heavy the carbohydrate content of the diet was made the blood sugar was not increased, though the glycosuria continued. This girl is now in perfect health.*

For subsequent data, see next page.

In certain cases in which glycosuria has been demonstrated repeatedly it seems eventually to clear up, although in such cases one should bear in mind that the urine may have been examined at intervals when it was sugar-free. One must remember that in many cases the glycosuria is post-prandial. This is well illustrated by the case of a little boy 3½ years of age (Case VIII, 124313), in which, during 1922, glycosuria was found repeatedly by his family physician. A low diet was prescribed, in spite of which the boy continued to show glycosuria

* For full report of this case see J. Am. M. Ass., 1922, 78, 103.

Subsequent data, Case VII. See page 123.

Date	1920	1921					
		July 27	July 28	Aug. 4	Aug. 5	Aug. 6	Aug. 8
Bl. Sug. mg/100 cc.....		125	84				100
Urine Sugar.....	1+	1+	1+	0	0	0	1+

Date	1921						
	Aug. 9	Aug. 10	Aug. 11	Aug. 12	Aug. 13	Aug. 17	Aug. 22
Bl. Sug. mg/100 cc.....				81			75
Urine Sugar.....	1+	0	0	0	0	1+	

Date	1921				1924 Oct. 10	1926 Jan. 27
	Aug. 23	Sept. 13	Oct. 4	Nov. 5		
Bl. Sug. mg/100 cc.....		73	77	129	122*	95
Urine Sugar.....	1+	0	0		0	0

* 3 hours after eating.

frequently, although there were periods during which he was sugar-free. In the belief that he was dealing with a diabetic condition the physician brought the boy to me on June 27, 1923.

There was nothing of significance in either the family or the personal history and the boy seemed perfectly well, the only abnormal finding being the glycosuria.

The summary of the findings, which is given below, shows that the blood sugar data are quite normal, so that diabetes can be definitely ruled out. The lad has remained in perfect health up to the present time without dietary restriction.

	1922		1923			1925	1926
Date	June 11	June 29	June 30	July 2	July 5	May 29	Jan. 21
Bl. Sug. mg/100 cc.			143	93	59	81	
Urine Sugar	1+	1+	0		tr.	0	neg.

CONCLUSIONS

1. Eight cases of non-diabetic glycosuria which are reported in this paper have been observed over periods ranging from two to eleven years, during which time the patients have not had diabetes.

2. These patients have had a full diet throughout the periods that they have been under observation.

3. The ages of these patients ranged from 2½ to 44 years at the time the glycosuria was discovered.

4. The literature on non-diabetic glycosuria includes reports of cases for varying periods up to 35 years, throughout which a normal status was maintained.

5. The highest daily excretion of sugar in the cases reported in the literature was 30 grams per day.

6. Observations of non-diabetic glycosuria show that it is an innocent anomaly requiring no restriction of diet or other treatment.

7. The importance of repeated examinations in cases of glycosuria which is supposed to be non-diabetic in character is emphasized, as is the necessity of glucose tolerance tests, in order to make sure that the glycosuria is not due to diabetic or a prediabetic condition.

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TREATMENT OF SENILE CATARACT WITH THYROID EXTRACT*

WM. J. KERR, M.D.; GEO. N. HOSFORD, M.D., AND H. C. SHEPARDSON, M.D.

From the Department of Medicine and Ophthalmology, University of California
SAN FRANCISCO

The medical treatment of senile cataract has interested ophthalmologists for at least a hundred years. A voluminous literature has accumulated and, in spite of much empiricism in treatment, a few noteworthy observations have been recorded. Aside from a small group of cases in which cataracts develop upon the basis of physical agents, such as intense light and heat, and trauma to the lens or adjacent structures, it is apparent that the common type of cataract is more intimately associated with general bodily disturbances. This disturbance is apparently related to metabolic changes as noted in the juvenile with tetany with probable alterations of the calcium balance, especially noted in endemic goitrogenous regions. Whether the parathyroid or thyroid glands are at fault is not clearly understood. Then we find a group of cases where the changes in the lens, and other structures of the eye, are associated with diabetes and frequently improve as the diabetes is brought under control. By far the largest group of cataract cases, however, is observed in individuals past fifty years of age, and are spoken of as senile cataract. The cataracts are of various types depending upon the location in the lens. These cataracts are practically always bilateral, one eye usually showing the process somewhat more advanced than the other, therefore indicating a general rather than a local cause. In this group also there may, from time to time, be variations in the cataract, depending upon the general health. Regression without treatment may be noted and the opacities may be stationary for years.

The individuals in whom the opacities appear show the bodily changes which are commonly called the signs of old age. The bodily changes are referable to all the embryonic tissues, but

* Read at the Tenth Annual meeting of the Association for the Study of Internal Secretions, Dallas, Texas, April 20, 1926.

those most readily observed are in the epidermal structures. The hair is usually thin, gray, dry and brittle; the eyebrows are thin, especially in the outer half, and tending to the formation of long bristles; the cilia are thin or wanting; the eye shows arcus senilis; the lens presents cataract. The bodily hair, especially in the axillary and pubic regions, is thin. The skin is dry and wrinkled, frequently thickened, and the sweat glands function poorly. The teeth show early destruction and loss. Keratosis, carcinoma baso-cellulare and epitheliomata are common. The nails are ridged longitudinally and are thin and brittle. In these individuals the mentality shows some impairment. The cardiovascular system is frequently the site of degenerative disease. The osseous system shows changes in the joints, particularly with the formation of Heberden's nodes, and chronic arthritis. The gastrointestinal tract may present disturbances associated with lack of hydrochloric acid in the stomach or there may be constipation. Renal impairment may be observed. Other conditions found in this group are reduced function of the internal secretion of the pancreas in diabetes; the formation of gall stones, diminished libido and many other disturbances generally associated with old age. It is also in this group that carcinoma appears to be more frequent.

Studies on the metabolic rate show very little to indicate that the metabolism, as represented by the oxygen-carbon dioxide exchange, is materially altered, although such individuals suffer from the cold. The present chemical studies on blood and urine show very little alteration from the normal, except in those cases with diabetes or renal disease. The calcium, magnesium, potassium, sodium and cholestrol metabolism need further study.

The changes in the ductless glands are not constant nor striking, but disturbances of function of single glands and alteration of balance of the related glands may be observed. The general bodily disturbances may be related to structural and functional changes in one or more of the ductless glands or the changes in these glands may represent only a part of the general picture of pathological old age.

We are indebted to Pollock (1923) for many of the early references on the medical treatment of cataract. In his review of the literature, the French are shown to have had the greatest enthusiasm in carrying out local and general medical measures

for treatment. Gondret (1829), is given credit for being one of the first to report the use of iodine preparations in the treatment of senile cataract. He used potassium iodide in large doses internally, alone and with tonics, and reported successful results. Others who followed used iodine or iodine salts in various ways, and also claimed improvement, and even cures in some cases. Notable among these early authors were Arlt (1854), who used an ointment containing potassium iodide, applied around the eyes; and Martin (1863), who employed iodides in eye lotions and drops.

In 1902 Würdemann reported three cases cleared by general treatment. Badal (1901), and in subsequent papers reported the control of opacities by eye baths, drops and lotions of potassium and sodium iodide and the subconjunctival injection of potassium iodide. He stressed the importance of early treatment. The injections were later used by Verderau (1904, 1906), DeWecker (1905), Boisseuil (1906), and von Pflugk (1906, 1908), but, although reported as successful, were later abandoned because of the pain of the procedure. There was some doubt whether the iodine could penetrate the lens, but its presence in the aqueous and vitreous humours which bathe the lens was demonstrated by Badal's assistants. Later von Pflugk (1908), presented experimental evidence that iodine could enter the lens after subconjunctival injection of potassium iodine solutions.

Von Pflugk (1906) gave a two-weeks' course of potassium iodide injections in various places around the cornea, followed by a course of dionin drops and a repetition of the course of injections. Wilkinson (1906) employed lithium and potassium iodide with tonics of iron and quinine and found no marked deterioration of vision under such treatment. In 1911 and 1913 Dor recommended baths of sodium iodide and calcium chloride based upon the assumption that nascent calcium iodide, if present, would be beneficial. He reported encouraging results in cases where the vision was not impaired more than one-half. Kaz (1912, 1914) reported successful results with Dor's method.

Schmidt-Rimpler (1908) used potassium iodide ointment and suitable glasses and felt that the opacities failed to advance in certain cases. Chevallereau (1912) reported further successful results with iodide eye baths and lotions.

Neeper (1908) and Connor (1909) reported improvement after dionin. Other substances used, about this time, with reported success were lens albumin by mouth by Römer (1908); lens extract by subcutaneous injections by Davis, thiocyinate by mouth and subcutaneous injections by Bernard (1909); resorcin by Elze (1909); mercury cyanide, one in four thousand, subconjunctivally, by Smith (1912) and Harry (1912); ion-iodide-electricity by Juan De Arana (1916) and Jones (1916) and others.

Koster (1913) used radium locally, probably in the treatment of secondary cataract. From 1918 to 1920 Cohen and Levin (1920) studied the effects of radium on cataract and reported improvement in 87 per cent of the cases. Franklin and Cordes (1920) found improvement in 84 per cent of cases after the use of radium.

Green and Green (1919) reported 58 per cent of improvement after using the Smith method of subconjunctival injections of mercury cyanide and subsequent eye baths of potassium iodide solutions and dionin drops.

Pollock (1923) recommended eye lotions containing potassium salts as the iodides, acetates, citrates and chlorides.

Harkness (1925), after reviewing the literature and the opinions of leading American ophthalmologists, reported that there was no specific treatment. He felt that with the various methods of treatment outlined above, the results were not uniform, and there had not been a sufficient number of untreated controls to warrant conclusions. He cited the growing disposition to regard senile cataract as a degenerative process associated with the general health of the individual. The more recent reports in the literature have emphasized the necessity of treating the patient from the standpoint of general metabolism.

Sanders (1925) again called attention to the importance of treating the patient generally as well as locally.

The relation between cataract formation and disturbances of the endocrine organs has been of increasing interest during the past twenty years. The thyroid and parathyroid glands have been the organs chiefly suspected, but the pituitary gland, pancreas, adrenals and ovaries have been cited as organs whose disturbed secretions may result in cataract.

Weeks (1906-7) mentioned a case of Gallan, where cataract occurred in myxedema, and a case of Landsberg (Centralbl. f. prakt. Augenheilk., 1888, S. 39) where cataract developed in association with choroiditis two years after the total extirpation of the thyroid. The case of Wagner (Graefe-Saemisch., Vol. XI, Part 1, p. 331, second edition) was also cited where neuroretinitis of both eyes was observed in a girl of 26 years with myxedema. Thyroidin was given and one eye improved in vision from 20/200 to 20/20, but in the other, in which optic atrophy was noted, there was no improvement in vision. The neuroretinitis was thought to be due to myxedema.

Dunn (1909-10) reported favorable results in the treatment of various eye conditions by the internal administration of thyroid extract. Improvement was noted in cases of cyclitis, interstitial keratitis, sub-acute glaucoma, corneal ulcer and chorioretinitis. Two cases of "rheumatic iritis" were reported, one in a lady of 75 years, who developed rheumatic pains three days after cataract operation, and in whom the pains ceased after thyroid medication. No specific mention, however, was made of the use of thyroid extract in the treatment of senile cataract.

Bennett (1913) reported a cure of recurrent hemorrhages into the vitreous in a young woman with retinitis proliferans after the internal administration of thyroid extract and calcium lactate. Other medication such as calcium lactate alone, mercury inunctions, potassium iodide, iron and tonics internally, and local x-ray treatments were used without results, before the thyroid extract was employed.

Risley (1913-14) reported two young patients who presented ocular conditions which were apparently associated with myxedema. In one case the cornea was vascular and showed a group of isolated gray spots, deeply situated, and in the other case there was a vascular keratitis and recurring superficial ulcers. Both improved greatly in general health and the local conditions showed rapid subsidence.

Lisser (1916) cited the results of treatment of interstitial keratitis by Risley, who found thyroid extract of value in the treatment of such cases. The thyroid was thought to be injured by the general infection, which in turn reduced the nutrition of the eye.

Edmunds (1916) reported the appearance of bilateral cata-

ract in a dog two years after total thyroidectomy. The dog had had convulsions, possibly tetany, following operation. Edmunds cited the case of Westphal who, in 1895, observed a female patient with total thyroidectomy. On the second day after operation tetany developed. In 1900 the patient was again admitted to the hospital in an apathetic state suffering from tetany and "epileptic fits." The symptoms were attributed to the removal of the parathyroid glands. Edmunds also cited the case of Schiller, where operation was performed in 1890 at the age of 36 years for the removal of a large goiter of long standing. Two days after operation tetanic spasms developed, and a few days later albuminuria without casts, edema of the hands, and mental dullness were noted. During the following year, six to eight months after operation, the tetany continued and cataract appeared in both eyes; the right eye was operated upon. The next summer, one year after operation, there was cachexia. The skin was dry, and the hair and nails fell out. A few months later the nephritis became acute and the patient died.

Jeremy (1919) reported post-operative cataracts in a case of goiter in a woman observed in 1914. Three or four months after operation vision began to fail. Both eyes showed opacities, the changes being more marked in one eye. The patient was stout and looked myxedematous, and complained of weakness and frequent tetanic spasms of the legs. Thyroid extract in tablet form relieved the symptoms of tetany, but the myxedema did not improve. The cataracts were attributed to a toxemia uncontrolled because of reduced thyroid and parathyroid secretion.

Dunn (1919) again called attention to the importance of the hypothyroid state in bringing about pathological changes in the eye. No mention, however, is made of the relation between cataract and the thyroid gland.

Szily (1921) pointed out the relation between tetany caused by the absence or dysfunction of the parathyroids and cataract. A number of authors of clinical and experimental reports are cited. Cataracts have been observed following thyroidectomy even when the parathyroids were preserved.

Kirkpatrick (1922) expressed the view that endocrine disturbances were responsible for primary cataract. The removal of the thyroid gland was not considered the sole cause of cata-

ract formation. The possible removal or injury of the parathyroid glands and the compensatory effort of other endocrine glands were considered of more importance in the etiology of cataract.

Zentmayer (1922) brought forth evidence that extirpation of the thyroid gland sometimes resulted in infiltration and ulceration of the cornea with partial blindness. Interstitial keratitis and bilateral cataract was also observed. Many of the convulsive disorders (convulsions of children and eclampsia) were attributed to parathyroid deficiency, and this deficiency was assumed to be an etiological factor in zonular cataract.

Fuchs (1922) stated that zonular cataract was due to hypofunction of the parathyroid glands. The statistics of Hesse were cited, where symptoms of tetany were observed in 81 per cent of all his cases of zonular cataract and in 41 cases of tetany zonular cataract was noted four times. Extirpation of the parathyroids in rats was followed by opacification of the lenses. Tetany in the adult was sometimes associated with the development of soft cataract. The correlation between cataract and parathyroid hypofunction was not clear and there was not enough evidence to show whether there was a direct action of certain chemical substances on the lens or an indirect nutrition disturbance by the intermediary action of the altered ciliary epithelium.

Burden-Cooper (1922) reviewed the subject of etiology of cataract and brought out the importance of the regressive changes in the body as the basis for senile cataract. The association of cataract with diabetes in younger individuals and the frequent occurrences of cataract with tetany was noted.

Hahn (1922) cited the eye conditions, such as falling of brows and lashes, eczematous lid inflammation, deep keratitis, certain types of cataract, uveitis, optic neuritis and retinitis pigmentosa, which are most often associated with hypothyroidism in the literature. This author felt that the variability of reports from thyroid administration in such cases showed that more must be learned about the cause of these conditions before a rational treatment could be instituted.

Schmitt (1922) pointed to endocrine disturbances as etiological factors in the production of uncomplicated cataract, but offered no specific data regarding treatment.

Van Zandt (1923), from his own experience, was relieved of a cataract of ten years' duration following the use of glandular therapy. Several preparations were taken by mouth, but the thyroid substance was probably the only potent one in the mixture.

Ascher (1924) reported therapeutic results in the treatment of cataract in women with ovarian extract. The spontaneous improvement in cases of cortical cataract was pointed out as likely to vitiate any but the most carefully controlled studies.

Hilroishi (1924) reported the results of extirpation of the parathyroid glands. This author found one parathyroid in each lobe of the thyroid in the rat. After their removal a mild course indicated the presence of accessory parathyroids. Half of the animals survived operation. Histological examination, when both parathyroids had been removed, showed that opacity of the lens occurred regularly; when one parathyroid was left opacity was found in only one case (25%). As a rule, the lens turbidity appeared simultaneously in both eyes, between the 7th and the 35th day after operation. There existed radial striae in the axial region, which spread toward the periphery, but did not render the entire lens opaque. This arrest of the process the author attributed to a cessation of the injury and a beginning functioning of the accessory parathyroids. Cataract formation was the most constant finding.

Jackson (1924) urged caution in drawing conclusions from treatment because of the natural tendencies of senile cataracts. He stated that the course of development is usually through many years, and that the process may become arrested or regression may take place, and the vision improve without treatment. This author urged general hygienic care and used no specific medication.

Taylor (1924) employed Dor's method of treatment for senile cataract, using an ointment of calcio-alkaline-iodid, which was less objectionable to use than an eye lotion or bath. Satisfactory results were reported, in early cases, where the treatment was continued without interruption greater than two weeks.

Our first interest was aroused in the medical treatment of senile cataract in 1921, when we (Wm. J. K.) noted the disappearance of opacities in the lens after the use of thyroid extract in the treatment of myxedema.

Upon being called to see a widow of 68 (Case 1) who, within a few days had been operated upon for senile cataract of the right eye, it was observed that there were many signs suggestive of a moderate myxedema. There was intense suffering from the cold. She was constipated. The hair was thin and gray, and the eye-brows were thin. The skin was dry and inelastic, and the nails were longitudinally ridged and brittle. The subcutaneous tissues of the arms proximal to the hands, and the legs proximal to the ankles, were rubbery and myxedematous. There were thick fat pads below the external malleoli and at the junction of the cervical and thoracic spine. The face was somewhat puffy. The systolic blood pressure was 180 mm. (mercury), and the diastolic pressure was 95 mm. (mercury). There were Heberden's nodes on the fingers and there was limited extension and deformity of the left elbow.

A competent ophthalmologist had described opacities in the left lens but did not feel that time for operation had arrived. The vision was definitely reduced, however, and the patient had not been able to read. Because of the symptoms and signs suggestive of myxedema, desiccated thyroid (Armour) one grain (0.065 gm.) twice daily, was started and the dosage was gradually increased until two grains (0.13 gm.) was being taken twice daily. It was impossible, at the time, to carry out any metabolic tests. Within two months the patient stated that the vision in the left eye, which had been greatly impaired, had returned almost to normal. On examination it was found that the opacities of the left lens had disappeared. There was at first some loss of weight associated with a diminution of the myxedematous tissue, and the skin became softer. The thin gray hair was gradually replaced by a very thick coat of dark hair and the eyebrows were restored to a more normal condition. About six months after the desiccated thyroid was begun, pains developed in the clavicles and the scalp became tender. A blood Wassermann, now taken for the first time, was strongly positive. Roentgenograms of the elbow, clavicles and skull showed luetic periostitis. The lesions disappeared under antiluetic treatment. The vision in the left eye remained unchanged and the general health of the patient was better than for many years. The desiccated thyroid was continued in small doses. There was no history of known luetic infection although the

husband had died suddenly many years before, at about fifty years of age, presumably from an aneurism.

In 1925, four years after the desiccated thyroid was begun, the vision in the left eye was practically normal and the lens showed only slight opacities at the periphery. Late in 1925 death occurred from an intercurrent infection. At autopsy the clavicle showed the healed luetic lesion. No other evidence of lues was noted. *The thyroid gland was small and practically replaced by fibrous tissue.*

Although in this case the cataracts were considered to be of the senile type, it is likely that lues was a factor in their production. The observations of the changes in the lens were incidental and incomplete for comparative studies. The lighting up of the periosteal luetic lesions after the use of thyroid extract was of interest.

The results with the first case appeared unusual, but we did not begin to make a more thorough study of senile cataracts and other eye conditions until another similar experience occurred. In 1923, the second patient (Case 2), female, age 60, came for examination, complaining of failing vision for eight years. An examination, by a competent ophthalmologist, revealed bilateral cataracts and corneal scarring. During the last two years the vision had failed rapidly and she had to give up work because of inability to get about alone. Only the largest newspaper type could be read. She could read better in a dim light. The physical examination showed a dry skin; the hair was gray, thin and dry, and the eyebrows thin on the outer half; cilia absent; nails thin, brittle, with longitudinal ridges. The axillary and pubic hair were very thin. Fat pads were marked at the junction of the cervical and thoracic spine and below the external malleoli. The subcutaneous tissues were of the myxedematous type. The blood counts, urine and stool were normal. A blood Wassermann was negative. The basal metabolic rate was not observed.

The treatment instituted was Armour's desiccated thyroid, one grain (0.065 gm.) a day for the first week; three grains (0.195 gm.) a day during the second week, and four grains (0.26 gm.) a day during the third and fourth weeks. On four grains a day there was slight evidence of toxicity. Later the

dosage was increased to six grains (0.4 gm.) a day without toxic symptoms.

There was definite improvement in vision within three months. Medium sized newspaper type could be read. There was less difficulty in getting about the street, and work had been resumed. Within four months the vision in one eye was said, by the patient, to be almost normal and the other eye had shown further improvement. The corneal scars were less marked. No accurate observations were made of the opacities at this time. The hair was getting darker and thicker and the eyebrows were returning to the normal condition. The cilia were practically normal. There had been at first a loss of weight but during the four months the loss had been regained. The subcutaneous tissues appeared more normal. There had been transient pains in the eyes during treatment.

One year after treatment was begun, the patient reported for examination upon request. She had not reported because she felt so well and had been working regularly. The vision had remained about the same as at the last examination. There was further improvement in the general condition. The desiccated thyroid had been continued with four grains (0.26 gm.) a day without toxic symptoms. An examination by a competent ophthalmologist showed opacities in the lens and some scarring of the cornea of both eyes. Exact figures for visual acuity before and after treatment were not obtainable, although there can be no doubt that there was improvement in the vision. It was also difficult to state whether the improved vision came from the clearing of the corneal scars or from the reduction of the opacities in the lens.

These isolated observations caused some inquiry into the literature. We found evidence, as stated above, of a possible relationship to disturbances of the parathyroid or thyroid glands. Also there was the frequent reference to the beneficial results from the use of iodine and its compounds. Whether the action of iodine compounds and desiccated thyroid is the same, is, of course, open to speculation.

We decided to combine the facilities of the Out-Patient Departments of Medicine and Ophthalmology in studying a group of cases of senile cataract. In most cases a careful history and physical examination were obtained. Routine urine examina-

tions, blood counts, blood Wassermann tests, chemical tests of the blood for non-protein and urea nitrogen, uric acid and creatinine and the basal metabolic rate were obtained. Later the blood chemistry studies and basal metabolic rates were not made as all were found to be within normal limits. The blood Wassermann tests were all negative. The physical examination in practically all cases showed the changes, with some variations, as described above.

The visual acuity tests were made under the ordinary lighting conditions of office and clinic and were subject to slight variations. The charts were always illuminated by the same degree of artificial light but the patients were in ordinary daylight. The observations were made at about the same time of day. The readings were taken under the most favorable conditions as to correction with glasses; that is, they were taken with their correction if the cataracts were not so advanced as to make all lenses useless.

No case was considered improved unless the patient could read a smaller line on the chart, although it is possible that this is within the limit of error.

Treatment was carried on by the use of Armour's desiccated thyroid alone, unless there were contraindications for the use of thyroid medication. The dosage was begun with one or two grains a day and gradually increased until toxic symptoms were produced in a few cases. Some patients required six to eight grains a day before showing toxic symptoms. In some instances toxic symptoms were produced without causing any changes in vision. Improvement in general health was noted in many cases in which the vision was not improved as well as in those cases in which vision was definitely improved.

There were many problems connected with the treatment of patients with cataract in the clinic. Most of them were below par mentally and co-operation could not be assured. Some patients came from a distance and it was not deemed wise to allow them to continue thyroid medication without proper supervision. A number of patients had incomplete records because of failure to return for observation. In these instances it is not known whether they were improved and for this reason failed to report, or whether they had become worse, as they could not be located. Other cases were excluded from the study because

of incomplete examinations of the eye. A third of our cases, covered by this report, were examined in the private office of Dr. W. S. Franklin, who has kindly consented to our use of his data. In some of these cases complete general histories and

TABLE I

Name	Age	Sex	Vision at Beginning		Vision Now		No. of Mo.	Dosage Grains	
			V. R. E.	V. L. E.	V. R. E.	V. L. E.			
C. T.	57	F	20/40	20/70	20/70	20/70	26	2–3	W
E. S. 68991	74	F	Lt. percept.	20/40	Lt. percept.	20/50	6	2–3	W
E. Sc. 107905	74	M	Fingers 5 ft.	20/100	Movement hand	20/100 Operated	6	1	W
F.Mc. 109824	54	M	20/50	20/200	20/40	Lt. percept.	9	3	W
O. D.	57	M	Fingers 8 ft.	Fingers 4 ft.	Lt. percept.	Lt. percept.	3	6	W
St.	34	M	20/50	Fingers 10 ft.	Operated		6	3–6	W
Ch.	40	F	20/40	20/40	20/70	20/70	23	3	W
L.	58	F	20/200	20/70	Operated		6	3	W
F. P.	69	F	Lt. percept.	20/30–2	Lt. percept.	20/30	17	2–3	S
S. Mc. 100418	61	F	20/70	Lt. percept.	20/70	Lt. percept.	8	3–4	S
M. De. 68152	54	F	20/70	20/70	20/70	20/70	7	3	S
S. 101629	60	F	20/20	20/30	20/20	20/30	13	1–4	S
J. C. 83079	75	M	Fingers 5 ft.	Fingers 5 ft.	Fingers 5 ft.	Fingers 10 ft.	30	1–3	S
M. St. 110029	58	F	20/20	20/40	20/20	20/40	28	1–3	S
P. R. 125839	63	F	20/70	20/50	20/70	20/50	7	1	S
M. F. 85419	65	F	20/30	20/20	20/30	20/20	13	1–3	S
Fr.	58	F	20/30	20/40	20/30	20/40	9	3	S
P.	57	M	20/40	20/40	20/40	20/40	3	3–5	S
H. T. 106929	65	F	20/40	20/200	20/30	20/70	3	2–3	I
F. G. 107843	66	F	Lt. percept.	20/70	Lt. percept.	20/50	10	3	I
M. S. 59762	57	F	20/40–2	20/40–2	20/30	20/30	23	3	I
J. P.	38	M	20/40	20/20	20/20	20/20	33	1–6	I
C. B.	82	M	20/70	Lt. percept.	20/40	Lt. percept.	11	1–3	I
W. L.	77	M	Fingers 5 ft.	20/70	20/200	20/40	6	1–4	I
C. M.	74	M	20/200	20/40	20/70	20/30	1	1–2	I
W.	55	F	20/20	20/200	20/20	20/100	9	3	I
C.	56	F	20/100	Amaurosis	20/70	Amaurosis	7	3	I
F.	67	M	20/30	20/40	20/20	20/20	23	2	I

Worse (W)—28.8%; Same (S)—35.6%; Improved (I)—35.6%.

physical examinations were not obtained, because of the reluctance of these patients to undergo such examinations. The condition of the circulatory system and the thyroid gland was, however, noted in these few instances.

Our small series of twenty-eight cases does not lend itself to a statistical study either as to type of cataract or as to the stage of the process. Table 1 shows the age, sex, comparative tests of visual acuity before and after treatment, the duration of treatment, and dosage of desiccated thyroid.

In the twenty-eight cases, ten, or 35.6 per cent, showed improvement; ten, or 35.6 per cent, were unchanged, and eight, or 28.8 per cent, became worse under treatment.

Two cases are worthy of special mention. One of these, not included in our table, was in a male of 47 years, seen first in November, 1923; he had had a bilateral cataract, with impaired vision in the left eye for five years and in the right eye for two years. At the time of examination the vision in the right eye was limited to light perception and the capsule of the lens had been needled twice during March, 1923, seven months before. There was incipient cataract in the left eye with 0.1 of normal vision. Glasses did not improve either eye. Examination revealed the lenticular material hanging in thick, white clouds in the eye upon which the needling had been done. The general and laboratory examinations were negative except for a trace of sugar in the urine, but the fasting blood sugar was only 0.082 per cent. Desiccated thyroid one grain (0.065 gm.) was begun three times a day. The patient did not return for six weeks and when he noted improvement the dose had been doubled. The clouds of lenticular material were practically entirely absorbed except for a few fibrous looking strands which projected from the periphery into the center where the lens had been. Two months later it was even clearer, and it was found that with a cataract glass he was able to read the 0.7 line with ease, and with a reading correction was able to read ordinary print. This striking result was attributed to the thyroid gland treatment, although the result may have been a coincident.

The other case of special interest was that of a widow, age 60, who was first seen in October, 1923, because of failing vision in the left eye. The vision was 0.5 in this eye and early opacities in the lens were noted. The general examination revealed the

signs frequently associated with old age. The heart was enlarged and there were presystolic and systolic murmurs at the apex, indicating mitral stenosis and insufficiency. The mitral valve lesion was probably based on attacks of chorea in childhood. No enlargement of the thyroid was observed. On thyroid medication, 1 grain (0.065 gm.) three times a day for two weeks and four times a day for the next two weeks, the opacities in the left lens entirely disappeared. The medication was continued for a fourth week, when an attack of auricular fibrillation developed. The medication was stopped. *Five months* later there was a definite enlargement of the thyroid gland with nodular areas and toxic symptoms were noted. At operation adenomata were removed. Since operation there has been no return of toxic symptoms. The attacks of auricular fibrillation have ceased. The opacities were not found at the time of the last examination.

In this case it is difficult to state which of the conditions was responsible for the auricular fibrillation. There was no doubt of the presence of mitral valve disease with moderate stenosis. In such cases auricular fibrillation is relatively common. The toxic adenomatous goiter, which was not noted at the first examination, rapidly increased in size or was made obvious by the loss of subcutaneous tissue about the neck, could easily have been the exciting cause for the attacks. The basal metabolic rate was normal before beginning treatment. Either of the above conditions should make one cautious in the therapeutic use of thyroid gland products.

DISCUSSION

In presenting this small series of cases, we are convinced that the thyroid gland preparation used improved the general health of the patient in most instances. Whether the improvement noted in vision, and the disappearance of the opacities is the result of the specific action of the thyroid substance administered or merely the result of improvement of the general condition, indirectly influencing the eye, we are unable to state. We feel that senile cataracts represent the local changes in the lens of individuals who are the subjects of general degenerative disturbances. This is strongly suggested by their appearance late in life, their bilateral occurrence and the tendency to vary

with the general health of the patient. While opacities may remain stationary for years, or may even clear up without treatment, thereby making it difficult to prove the value of any therapeutic procedure, we feel that these very facts should encourage us to renew our efforts along more general lines of investigation. Such studies must be made on a large series of cases, with ample untreated control and the types of cataracts must be clearly differentiated.

From our studies, we are unable to state that any particular type of cataract responded better to treatment than another. We were dealing, for the most part, with advanced cases, in which we could not expect much improvement. The incipient cases offer better hope of cure. The responsibility for initiating future investigations rests with the ophthalmologists, who may discover peripheral changes in the lens before there is any definite reduction in the visual acuity. These changes in the lens are noted when refraction is done. A warning, however, should be sounded for the ophthalmologist who may enthusiastically begin the administration of thyroid substance or other drugs without having full knowledge of the general condition of the patient. Here is an opportunity for close co-operation between the ophthalmologist, who may see the patient first, and the internist who is better able to decide when general treatment should be instituted and to follow the patient through the period of administration.

The use of iodine or its compounds in the past, both locally and generally, has been shown to be of value in the treatment of senile cataract. The action of the iodine is not as yet clearly understood. It is supposed to have an action in removing fibrous tissue generally. The action may be through an activation of the thyroid gland and the action of the iodides and thyroid substance may be the same. The general circulation may be improved by these substances and in this way the local circulation and nourishment of the eye may be stimulated. Such therapeutic agents as radium, x-ray, mercury cyanide and others may also increase the local circulation and metabolism of the eye to bring about improvement.

We feel that one may expect better results in early senile cataract if the iodides are used locally in the eye and thyroid substances or the iodides are given internally. Further studies

are needed on the metabolism of sodium, potassium, magnesium and calcium in relation to the changes in the lens in senile cataract. The work of Burge (1918), who showed that in the cataractous lens the potash is reduced to 9.8 per cent from the normal of 38 per cent, and the calcium is increased from a negligible quantity of 0.08 per cent to 15 per cent, is of interest. The increase of magnesium was found to be less marked, but definite.

When the metabolism of cholestrol is better understood we may find a relationship between it and the formation of cataract in the senile as well as in the diabetic patient.

The frequent occurrence of tetany, with disturbed calcium balance, parathyroid or thyroid disease and cataract formation, indicates a definite relationship. The endocrinologist should cooperate in this field of investigation.

There is no great danger in the administration of thyroid substance, if the patients are carefully studied before treatment and watched for toxic symptoms. Improvement was noted in most of the cases benefited before any toxic symptoms appeared. The basal metabolic rate was within normal limits in practically every case, and in a few was toward the lower limit of normal. We do not feel that a normal metabolic rate contraindicates the use of thyroid medication, if it is carefully supervised. We have been using small doses of thyroid substance, for many years, as a general tonic, and have been pleased with its beneficial effects. In this we have felt that the action of the drug was probably similar to that obtained with small doses of the iodides.

We have employed thyroxin in a few cases of advanced senile cataract, but the results have not, thus far, been striking. Parathyroid hormone is being tried, under the direction of Dr. H. Lisser, and may be the subject of separate report.

Other eye conditions have been treated with thyroid substance. In some cases of corneal ulcer, intractible to ordinary methods of treatment, the improvement has been prompt and striking. In glaucoma we have not had the opportunity to study the cases long enough to determine the possibility of improvement.

We wish to think Dr. W. S. Franklin, Clinical Professor of Ophthalmology, for his co-operation and suggestions.

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STUDIES OF THE THYROID APPARATUS. XXXIV. THE RÔLE OF THE THYROID APPARATUS IN THE GROWTH OF THE HYPOPHYSIS

FREDERICK S. HAMMETT

The Wistar Institute of Anatomy and Biology

PHILADELPHIA

INTRODUCTION

From the point of view of the age relations the several incretory organs studied in this investigation exhibit individual and characteristic growth associations with thyroid and parathyroid function. It, therefore, seems best to discuss the response of each of the glandular deficiencies initiated at the stated ages (23, 30, 50, 65, 75 and 100 days), in separate papers, rather than to bring them all together into a single report such as was made for the 75 and 100-day-old series (1) (2). A group comparison will be a legitimate subject for a later summarizing interpretation.

It is not necessary to go into the plan, scope and methods of the study as a whole. These are to be found in preceding papers. It should be noted that the computation of the initial adjusted values from the observed reference control figures differs from that previously employed (3). The observed mean weights and their probable errors of the hypophysis of the several groups of rats are given in Table 1. Table 2 contains the absolute percentage increments in weight and the percentage rate of growth of the organ in the test groups in terms of that of their controls. To facilitate study by visualization the essential comparisons are presented in three charts. The flat black columns represent the growth of the hypophysis in the controls. This is always 100 per cent. The open columns represent the growth of the organ in the tests. The order of sequence is given by the superscript. For reasons given elsewhere (4) the reaction to thyro-parathyroidectomy is interpreted in terms of thyroid deficiency alone.

THE EFFECT OF THYROID DEFICIENCY

On Chart 1A the growth of the hypophysis in the male rats is compared with that of the body in weight after thyroid removal at the stated ages. It is evident that the reaction of the gland to thyroid deficiency is quite different from that of the body as a whole. An acceleration instead of a retardation of growth has been induced. No evidence of a pubertal influence is noted.

From Table 1 it is seen that the weight of the hypophysis of the male tests is greater than that of their controls. This is evidence of an absolute hypertrophy.

On Chart 1B the growth of the hypophysis in the female rats is compared with that of the body in weight after thyroid removal at the stated ages. It is evident that the organ is not retarded to anywhere nearly the same degree as is the body as a whole. Acceleration of growth follows thyroid removal at 65 days of age. This is indication that puberty is a factor in determining the reaction in the female. Although there is a hint that the period of pubertal adjustment determines a tendency to parallelism of the hypophysis with the body weight in the direction of change in degree with the change in age at time of thyroid removal, yet here as in the male the general picture indicates that the response of the gland is distinct in type as well as in degree from that of the body.

From Table 1 it is seen that absolute hypophyseal hypertrophy only occurs in the female when the thyroid is removed at 65 days of age.

The data justify the conclusion that the growth of the hypophysis is specifically influenced by thyroid deficiency.

From this the natural deduction would be that there is a specific thyroid-hypophysis incretory relationship. There are certain facts which seem inconsistent with this deduction.

A biometrical analysis of the weight interrelations of the glands of internal secretion has been made by the method of partial correlation (5) from the values furnished by the organ weights of 121 of the male and 121 of the female rats which served as controls in the thyroid studies. This use of the same material for the two types of investigation enhances the validity of the interpretations.

TABLE I

THE OBSERVED MEAN WEIGHT OF THE HYPOPHYSIS (IN GRAMS) OF THE SEVERAL GROUPS OF RATS

"Beginning" values for "Control" and "Test" groups computed according to method referred to in the text.

	THYROPARATHYROIDECTOMIZED					PARATHYROIDECTOMIZED			
Age Series	At Beginning			At End (150 days)		At Beginning		At End (150 days)	
	Ref. Contl.	Contl.	Test	Control	Test	Contl.	Test	Control	Test
	MALES								
23	0.0017±0.0001	0.0018	0.0017	0.0083±0.0002	0.0098±0.0005	0.0017	0.0017	0.0081±0.0002	0.0064±0.0001
30	0.0023±0.0001	0.0022	0.0022	0.0082±0.0003	0.0093±0.0003	0.0023	0.0023	0.0088±0.0002	0.0066±0.0001
50	0.0034±0.0001	0.0033	0.0033	0.0081±0.0003	0.0097±0.0005	0.0033	0.0033	0.0079±0.0002	0.0063±0.0001
65	0.0045±0.0001	0.0043	0.0043	0.0080±0.0002	0.0090±0.0003	0.0044	0.0044	0.0087±0.0001	0.0066±0.0002
75	0.0049±0.0001	0.0047	0.0048	0.0084±0.0003	0.0096±0.0003	0.0048	0.0047	0.0078±0.0002	0.0057±0.0002
100	0.0059±0.0002	0.0058	0.0058	0.0072±0.0001	0.0082±0.0003	0.0058	0.0057	0.0072±0.0001	0.0063±0.0002
	FEMALES								
23	0.0020±0.0001	0.0019	0.0019	0.0109±0.0002	0.0106±0.0002	0.0020	0.0020	0.0108±0.0003	0.0082±0.0003
30	0.0024±0.0001	0.0023	0.0023	0.0108±0.0006	0.0110±0.0003	0.0024	0.0023	0.0110±0.0004	0.0092±0.0003
50	0.0040±0.0001	0.0038	0.0038	0.0107±0.0004	0.0092±0.0005	0.0040	0.0039	0.0104±0.0003	0.0084±0.0003
65	0.0052±0.0003	0.0051	0.0049	0.0098±0.0003	0.0112±0.0004	0.0051	0.0050	0.0100±0.0003	0.0091±0.0005
75	0.0057±0.0002	0.0055	0.0055	0.0103±0.0003	0.0102±0.0005	0.0054	0.0054	0.0095±0.0004	0.0077±0.0004
100	0.0072±0.0002	0.0070	0.0070	0.0104±0.0004	0.0091±0.0003	0.0070	0.0069	0.0104±0.0004	0.0083±0.0003

TABLE II

THE ABSOLUTE AND THE RELATIVE PERCENTAGE RATE OF GROWTH OF THE HYPOPHYSIS OF THE SEVERAL GROUPS

THYRO-PARATHYROIDECTOMIZED GROUPS

PARATHYROIDECTOMIZED GROUPS

	MALE			FEMALE			
	Thyro-parathyroidectomized Groups						
Age Series	Control–%	Test–%	T/C	Control–%	Test–%	T/C	CM*/CF*
23	366.3	466.5	127.3	473.7	457.9	96.7	77.3
30	272.7	322.7	118.3	367.5	380.4	103.5	74.2
50	145.5	193.9	133.3	181.6	142.1	78.3	80.1
65	86.1	109.3	127.0	92.2	128.6	139.5	93.4
75	78.7	100.0	127.0	87.3	85.5	97.9	90.1
100	24.1	41.4	171.4	48.6	30.0	61.8	49.6
	Parathyroidectomized Groups						
23	368.2	281.0	76.3	440.0	310.0	70.5	83.7
30	282.6	187.0	66.2	368.1	298.3	81.0	76.8
50	139.4	90.9	65.2	160.0	115.4	72.1	87.1
65	97.7	50.0	51.2	96.1	82.0	85.3	101.7
75	62.5	21.3	34.0	75.9	42.6	56.1	82.3
100	24.1	10.5	43.6	48.6	20.3	41.8	49.6

* C.M., control male; C.F., control female.

A study of the distribution of the thyroid weight values showed that these were divisible into two groups (6), a group of normal (or usual range) and a group of heavy thyroids. On the basis of the analysis of the correlation between the first group and their respective body weights and the second group and their respective body weights, the conclusion was drawn that the first group represented thyroids of normal (or usual) range of activity, and the second represented thyroids of enhanced activity. The biometrical analysis of the weight interrelations of the incretory organs was therefore similarly classified.

It was found that within the usual range of thyroid size there is no valid degree of weight association between hypophysis and thyroid in the adult rat (150 days of age) when the general factors for organ size carried by the body weight

and the assumed influences for organ size exerted by the other incretory organs are held constant by appropriate statistical treatment. The fifth order correlation coefficient in the male is 0.042, and in the female 0.127.

Although there is a valid positive association between the two glands when the general factors of influence are in force, this is largely due to the body size factor, since when this is held constant by the method of partial correlation the zero order coefficients of 0.371 ± 0.062 for the male and 0.299 ± 0.067 for the female drop to 0.112 and 0.129, respectively. Consistent with this dependency of the thyroid-hypophysis association on the body size, is the fact that the correlation between hypophysis and body weight is high and positive, being 0.701 ± 0.031 in the male and 0.515 ± 0.045 in the female.

These results are apparently at variance with the idea of a specific incretory relation between thyroid and hypophysis, since they show definitely that within the normal (usual) range of thyroid size and presumably activity the shifts therein are not productive of shifts in weight of the hypophysis, which are independent of shifts in body weight. That is to say the shift in hypophysis weight which occurs with shift in thyroid weight (activity) is not due in this group to a specific relation between thyroid and hypophysis, but is due to the relation of the hypophysis to the effectiveness of the general body factors as related to thyroid activity (weight).

Now, not only does complete thyroid deficiency bring out a specificity of reaction on the part of the hypophysis, which is not exhibited under usual conditions, but a like phenomenon is exhibited when thyroid activity is above the usual.

While the literature, summarized by Cameron and Carmichael (7), gives evidence of pituitary hypertrophy on thyroid feeding, more definite information in this direction is had from the pertinent weight correlation coefficients derived from the heavier than usual thyroid weights of my control rats. These show that there is a high degree of positive correlation between the heavier or more active than normal thyroid and the hypophysis which is independent of the general factors for size carried by the body weight. The first order coefficient obtained when body weight is held constant is 0.452 in the male, and 0.653 in the female, as against the zero order values of 0.117 ± 0.112

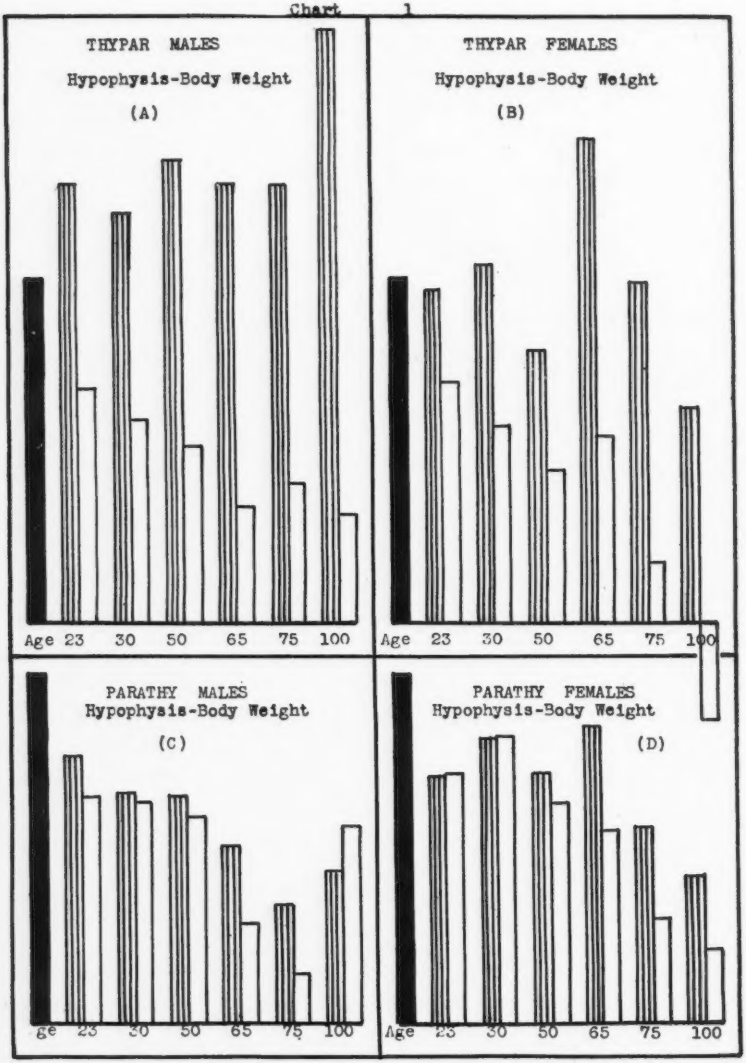

Chart 1. The growth of the hypophysis compared with that of the body in weight. A—Thyro-parathyroidectomized males. B—Thyro-parathyroidectomized females. C—Parathyroidectomized males. D—Parathyroidectomized females. Order of sequence given by the superscript.

and 0.399 ± 0.092 for the two sexes, respectively. Further stabilization for the influences assumed to be exerted by the other incretory organs does not alter significantly the first order values.

The conclusion is that there is a specific weight association between the hypophysis and the mildly overweight thyroid. The natural deduction from this would also be that there is a specific incretory relation between hypophysis and overweight thyroid.

Indirect evidence in support of the general conclusion is had from the fact that the growth response of the hypophysis to the condition of essential undernutrition induced by parathyroid removal (4) is the same in type as that of the body as a whole (Chart 1C and D), and similar to that reported in conditions of undernutrition produced by dietary deficiency (8) (namely a retardation of growth), whereas its response when the same fundamental state of undernutrition is produced by thyroid deficiency is an hypertrophy or virtual independence of the general body response. This indicates the presence in this case of a dominating factor which is not present in the others, the nature of which can be no other than a specific thyroid-hypophysis incretory relationship.

From these data it is evident that the size of the hypophysis is related to thyroid activity only when this passes the limits assumed to be normal in either direction. The lack of weight correlation within the usual range of thyroid size leads to the inference that there is no incretory interrelationship under these conditions. The objection might be raised that expression of weight association between the two glands is prevented by an arithmetical balancing of the results (tendency to hypophyseal enlargement) of the extremes of thyroid activity, were it not for the fact that a positive weight association exists which is dependent on body size. Such being the case it is probable that the lack of specific weight correlation within the usual range of thyroid size and activity is due to the fact that the hypophysis, like the other organs, is dependent on the effectiveness of the total growth of the body, in which the thyroid plays no specific rôle aside from its part in the regulation of the metabolic level (4). Under normal conditions it might well be that no expression would be given of any specific hypo-

physis-thyroid incretory relation in so far as size association is concerned. Indeed it may be that no incretory relation is in force under usual conditions, and that this only comes into play in conditions of organic imbalance when thyroid activity passes the normal limits in either direction. In other words, it is probable that the specific dependency of the hypophysis is potential or dominant under usual conditions of thyroid activity, and only comes into action to be expressed as an enlargement and possibly an enhancement in function when thyroid activity exceeds the usual limits.

The actual functional significance of the specific incretory association between thyroid and hypophysis is unknown. Since conjectural interpretation is at all times permissible, I will outline what to my mind appears to be the most probable basis of the relationship from the data at hand. This is done with the decided understanding that the matter at the present time is solely in the speculative stage, that the opinions expressed are purely tentative, and that their sole utility is to serve as a foundation for further work leading to ultimate clarification.

The studies of Kojima (9), Smith and Smith (10), Loeb and Kaplan (11), Flower and Evans (12) and others show pretty definitely that the anterior lobe of the hypophysis is the part of the organ which is concerned in the thyroid-hypophysis incretory association. The cumulative experience of many investigators has established the fact that a function of the anterior lobe of the hypophysis is concerned in growth. This work beginning with Cushing (13) and continuing with Robertson (14) down to the recent startling results of Evans (15) and his collaborators is too well known to need extensive citation.

The problem is thus narrowed down to a consideration of the respective rôles of the thyroid and the anterior lobe of the hypophysis in growth. The reader will note that I write of the "respective" and not of the "replacement" rôles of the two organs in this phase of physiological activity. This is because the work of Smith and Cheney (16) and others as discussed in earlier papers (1) (2) has effectually disposed of the idea that the hypophysis functions vicariously for the thyroid when this is lacking. The fact that there is no correlation between growth retardation in body weight and growth reaction of the hypophysis to thyroid removal at the different ages (shown in Chart

1A and B) is consistent with the idea of the inadequacy of the once-held opinion.

In the paper which dealt with the interpretation of the rôle of the thyroid in growth (4) it was pointed out that there are two types of growth: e. g., growth by increase in cell mass and growth by increase in cell number. It was also pointed out that since growth is a process of energy utilization, it is capable of being expressed in terms of intensity and capacity factors. The analysis of the data led to the conclusion that the rôle of the thyroid in growth is that of a determinant of the capacity factor, that the intensity factor is largely regulated by catalysts other than those produced by the thyroid, and that the thyroid is more largely concerned in growth by increase in cell mass than in growth by increase in cell number. A comparison of body growth in weight and length (17) and the study of the growth of the reproductive system of the same thyroidless (18) animals substantiate the interpretation.

Now it is obvious that while it is convenient and even necessary for purposes of analysis to subdivide the phenomenon of growth into its various aspects, all the several phases are interdependent and no strict mathematical delimitation is possible. It is only the question of more and less, not of how much, that can be answered at the present time.

It can be assumed that the hypophysis is concerned either in growth by increase in cell number or in the intensity factor of growth or in both.

Supporting the first conception is the skeletal overgrowth of acromegaly, a condition associated with hyperfunction of the anterior lobe of the hypophysis. Consistent with the second is the adiposity of hypofunction of this part of the gland in man. For a diminution in the intensity factor of growth, with thyroid function persisting, might well result in a relative increase in the capacity factor which would be expressed in a relatively greater than normal growth by increase in cell mass.

The results of the administration of anterior lobe extract to thyroidless rats by Flower and Evans (12) led them to imply that thyroid deficiency conditions an underfunctioning of the hypophysis. This conclusion, I believe, will eventually be modified.

Chart 1A and B shows that the hypophysis of the thyroidless rats of both sexes is larger per unit body weight than that of the controls. In all groups of males the organ is even absolutely heavier in the tests than in the controls, notwithstanding the lesser body weight, and in 66 per cent of the groups of females it is either the same or heavier in the tests than in the controls.

It may well be that the absolute functional capacity of the hypophysis in the 30 and 100-day-old series of the females is less than normal, indeed it may be that the hypertrophied organ is less functionally active per unit body weight. All experience with physiological and non-pathological enlarged organs speaks against such a view. Yet reasoning by analogy is no proof, nor can proof be given at the present time by measurement of output. Therefore if Flower and Evans choose to stand by their guns it will be difficult to dislodge them on a basis of direct observation. It is possible, however, to bring forward an alternative hypothesis which is consistent with the valid observational data at hand. But before going on to this let us see whether or not my results are consistent with the assumption that the hypophysis is concerned in growth by increase in cell number and in the intensity factor of bodily increments.

As the animal grows older, growth by increase in cell number is a decreasing proportion of total growth, and growth by increase in cell size (mass) is an increasing proportion. Hence on the assumption that the hypophysis is directly concerned in the former the part played by the organ in growth decreases with age by virtue of the natural limitations of the organism, while that of the thyroid increases by virtue of its being a large determinant in growth by increase in cell size. Therefore thyroid removal at progressive stages of development would deprive the organism of a stimulus of relatively increasing importance for growth, while at the same time the capacity for response of the body to the hypophyseal stimulus is decreasing. The result would naturally be an increase in growth retardation with increase in age at time of thyroid removal. If on the other hand thyroid deficiency conditions an underfunctioning of the hypophysis with respect to growth, it would be expected that the effect of this on growth would be most marked at the

age of maximum intensity, or in the younger animals, with a consequent greater or equal retardation in the younger than in the older age series. If this does not happen it would be expected that the effect of the hypophyseal stimulus to growth by increase in cell number would be greatest at the earlier ages, and that this would be expressed by a lesser retardation in the rats thyroidectomized at the younger than at the older ages, when the ability to respond to the stimulus is reduced. Since this is what occurs, observation is consistent with assumption. Such consistency, however, is not proof.

The assumption that the intensity factor of growth is largely determined by the hypophysis in the thyroidless rats is supported by the growth capacity curves for body weight of these animals (4). It was pointed out in their analysis that the values fall below the normal immediately after thyroid removal, but soon recover and follow the normal course with age, both in degree and type. That is to say the intensity factor as represented by grams increment per unit mass per unit time is normal for the age. If the above assumption is correct this is what would be expected. The first effect of the lowered metabolic level consequent upon thyroid removal would be a lowering of the level of functional activity of the hypophysis as well as of the rest of the body. The value of the intensity of growth would then fall below the normal. The specific incretory relation of the thyroid to the hypophysis exhibited in conditions of thyroid dysfunction produces an hypertrophy or inhibition of growth retardation of the latter with the result that its activity is greater than normal per unit mass of body tissue. Then and if the hypophysis is concerned in the intensity factor of growth, the relative increase in growth stimulus given by the hypophysis would tend to counterbalance the general decrease in the ability to respond, due to the lowered metabolic rate and the intensity factor would be brought back towards the normal level. Fact is seen to be consistent with assumption. The correctness of the latter is, however, not to be established by these observations alone. They are merely suggestive indices pointing the way to ultimate solution.

The validity of the assumption should not be attacked on the basis of the fact that a like tendency of adjustment of the intensity level of growth to the norm occurs in the parathyroidless

groups. Here the thyroid is active along with the hypophysis. Although the intensity factor is undoubtedly regulated by catalysts other than those produced by the thyroid, when these are absent, it is by no means to be considered that this is uninfluenced by them when present. Nor must the idea be had that the thyroid is the sole regulator of the capacity factor of growth. It certainly is not the only determinant of the metabolic level, for metabolism and growth in mass proceed after the thyroid has been removed. The two phases of growth are interrelated and interdependent. This does not preclude their separation in analysis, nor destroy the validity of the argument that the one is regulated by a different set of catalysts than the other. The facts show that the thyroid is a major determinant of the value of the capacity factor (4). Inference leads to the idea that the hypophysis is the chief regulator of the intensity factor. Whether this will be established as fact remains to be seen.

Now Flower and Evans (12) report that normal growth of thyroidless rats is preserved when these are treated with anterior hypophyseal extract. They suggest that the growth dystrophies of thyroid deficiency may be referable to anterior hypophyseal underfunctioning resulting from the thyroid lack, and that the growth resumption which obtains on thyroid therapy is due to the reestablishment of normal hypophyseal function. An alternative explanation of their results is as follows:

Due to the interdependency of the intensity and capacity factors of growth it is obvious that a positive stimulation of one would, other things being equal, produce a positive change in the expression of the activity of the other. A negative stimulation of the one would similarly produce a negative change in the expression of the other. This is what occurs immediately after thyroid removal. Soon, however, the intensity factor recovers and becomes the value characteristic of the age, notwithstanding the fact that the capacity factor is still below the normal level. Since the only other organ of known specific importance to growth is the anterior lobe of the hypophysis, and since the hypophysis hypertrophies after thyroid removal, thus indicating increased functional activity per unit body mass, the natural assumption to be made is that a function of the anterior lobe of the hypophysis is largely concerned in the regulation of the intensity factor of growth.

Granting the assumption, the administration of anterior hypophyseal extract to thyroidless or even to normal rats would result in an absolute increase in the stimulus to the intensity factor. This in turn would result in a raising of the absolute level of the capacity factor, the extent of which would depend on the amount and efficacy of the administered stimulus, and the expression of which would be an increased growth in body weight. Thyroidless animals could well be brought to the normal growth level by such a procedure. My thyroidless rats did not reach normal growth in mass (grams per day) because the intensity factor was not artificially stimulated by the administration of anterior hypophyseal extract. The detailed exposition of the process of recovery of the intensity factor is given in an earlier paper (4) and need not be repeated.

It is thus evident that the conception of Flower and Evans (12) is unnecessary and not in accord with the data as a whole.

The resumption of growth in thyroidless rats to which thyroid preparations are given is not due to an increase in anterior hypophyseal function. It is an expression of the fact that such treatment raises the metabolic level, raises the ability of the tissues as a whole to work over more materials, raises the level of the materials available for growth, and raises the rate at which these are incorporated into the body. That is to say, the capacity factor is brought back towards its normal level and growth as expressed by grams increment per day is enhanced. The introduction of the hypophysis into the picture as a dominant factor is unnecessary.

Turning now to consideration of the response of the hypophysis to thyroid deficiency in the female it is seen from Chart 1B that there is a tendency for the direction of change in degree with change in age at time of thyroid removal to be the same as that exhibited by the body weight from puberty (65 day old series) onward.

From the discussion of the preceding paper (18) this phenomenon is taken as indicating a dependence of the response on the effectiveness of the general growth processes of the body, and a virtual independence of the organ from the thyroid in any specific sense.

At first sight, then, this response of the hypophysis of the female would seem to be inconsistent with the general principle

Chart 2

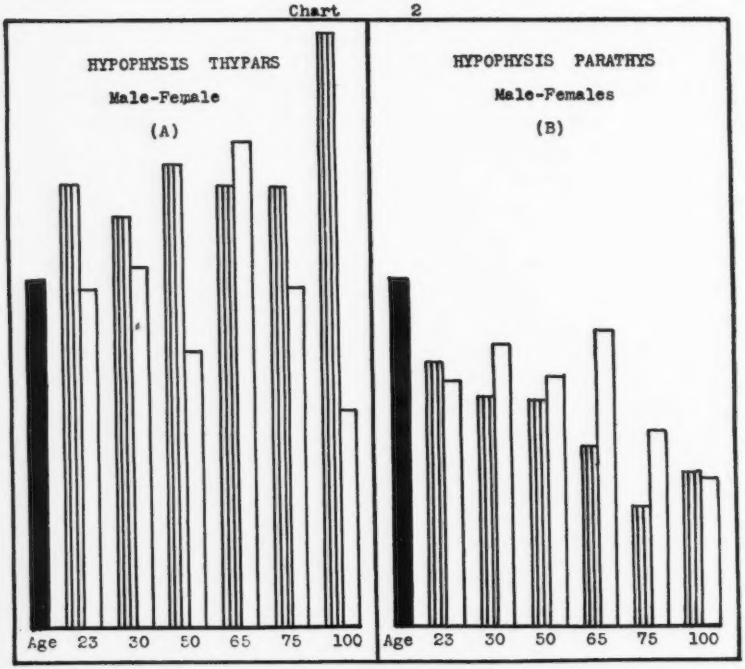

Chart 2. The growth of the hypophysis in the male compared with that in the female after A—Thyroid removal, and B—Parathyroid removal at the stated ages. Order of sequence given by the superscript.

if the idea of a specificity of relationship with the thyroid is valid. Such an apparent paradox demands clarification. Fortunately the necessary data are available.

The age of 65 days is the approximate time of first appearance of corpora lutea in the ovaries of the Wistar albino rats (19). This is obviously the period of the first surge in incretory activity of the ovary. From Chart 1B it is seen that the coming into play of this new factor is accompanied by a marked change in the response of the hypophysis to thyroid removal. Not only does the course of change with age tend to parallel that of the body in weight, but it is at this time alone that thyroid removal is followed by hypertrophy of the hypophysis.

The natural conclusion is that these shifts are conditioned by the incretory activity of the ovary. Such a conclusion is

justified not only by the immediate data, but also by the correlated data given in preceding papers of this series, by the data afforded by the studies of the chemical differentiation of bone during growth (20) (21) (22), and by the pertinent correlation coefficients of the adult animal.

The weight correlation between hypophysis and ovary is 0.443 ± 0.049 when the general factors for organ size carried by the body weight and the influences assumed to be exerted by the other incretory glands have not been held constant by the method of partial correlation. Although the value drops to 0.223 when body weight is held constant it is still positive and valid. This shows that there is a weight association which is independent of body size. Correlating this with the fact shown in the preceding paper (17) that the growth response of the ovary to thyroid deficiency is almost entirely due to its dependence on the effectiveness of the general growth processes of the body, it is clear that the parallelism of the hypophysis with the body in weight is determined by its weight association with the ovary, rather than by its dependence on the growth factors of the body as a whole. That is to say, the ovary is the determinant of the post-pubertal parallelism of the response of the hypophysis and body weight to thyroid deficiency.

It is therefore evident that the reaction of the hypophysis in the female is not inconsistent with the idea of a specific incretory relationship of this gland to thyroid disturbance.

Turning now to the sex comparison it is seen from Chart 1A that no evidence of pubertal influence on hypophyseal reaction is present in the males. Consistent with this is the fact that there is no weight association between testis and hypophysis in the adult male when body size influence is held constant. The first order coefficient is —0.010.

The consistency of the data leads to the conclusion that the incretory relationship between thyroid and hypophysis in the male is largely uninfluenced by gonadal incretory activity. Hence the intervention of the gonad in the female is a sex-specific phenomenon.

Further sex-specificity is shown on Chart 2A where the response of the hypophysis of the males is compared with that of the females at each of the stated ages. It is seen that regardless of direction the degree of response is greater in the male than in

the female in all save the 65 day old series. Moreover, consistent hypertrophy of the hypophysis follows thyroid removal in the male but not in the female.

A similar trend of sex difference in response follows thyroid feeding. Hoskins (23) found that under such conditions the hypophysis of the male tends to be heavier while that of the female tends to be lighter than the normal control. The combined observations of Herring (24) and Hewitt (25) are in agreement with the findings of Hoskins.

These facts indicate that the specific relation of the hypophysis to thyroid disturbance is less influenced by sex-conditioned factors in the male than in the female. Consistent with this conclusion is the fact that there is no specific gonad-hypophysis weight relation in the normal adult male, while in the female a small but validly positive association exists. The 5th order coefficient is -0.070 ± 0.051 in the male and 0.151 ± 0.049 in the female.

THE EFFECT OF PARATHYROID DEFICIENCY

On Chart 1C and D the growth of the hypophysis is compared with that of the body in weight after parathyroid removal at the stated ages.

It is seen that the growth of the gland is consistently retarded in both sexes in all groups. The course of the change in degree of retardation with change in age at time of the initiation of the parathyroid deficiency is quite the same for the hypophysis as for the body weight in both sexes save in the 65 day old series of females. This parallelism is proof that the growth of the hypophysis is not specifically related to parathyroid activity, and that the retardation which occurs is due to the dependency of the organ on the effectiveness of the growth processes of the body as a whole.

Consistent with this is the fact noted earlier that the coefficient of correlation between hypophysis and body weight is high and positive in the adult rat of both sexes.

There is a general trend for the retardation of the hypophysis to be less than that of the body weight. This difference is merely the expression of the characterizing difference in the metabolic processes concerned in growth of the hypophysis from

those of the body as a whole with respect to the lowered nutritional level produced by parathyroid deficiency. It is not due to any hypothyroid condition, for as Table 3 shows, the weight of the thyroid per unit body weight of the tests is not consistently different from that of their controls of the same age series.

The degree of difference is most marked at and after puberty in both sexes. This increase is further evidence for the belief stated in previous papers that the onset of sexual maturity determines profound changes in the physiological processes of all parts of the body.

The non-conformity of the organ with the body weight in the females of the 65 day old series is attributable to the specific incretory relation between ovary and hypophysis. This relation

TABLE III

THYROID WEIGHT PER UNIT BODY WEIGHT OF THE PARATHYROIDLESS RATS AND THEIR CONTROLS. THE VALUES FOR THE THYPAR CONTROLS ARE ALSO GIVEN TO SHOW THE NORMAL VARIATION. ALL VALUES FROM RATS 150 DAYS OF AGE.

	MALES			FEMALES		
	Controls		Tests	Controls		Tests
Age Series	Thypar*	Parathy*	Parathy	Thypar	Parathy	Parathy
23	1.03	1.12	1.16	0.96	0.94	0.89
30	0.74	0.77	0.69	0.89	0.96	0.88
50	0.88	0.89	0.78	1.11	0.96	0.95
65	1.02	0.91	0.82	1.01	0.94	1.00
75	1.33	0.86	0.90	1.31	1.03	1.04
100	0.90†	0.90	0.93	0.97†	0.97	0.87

* "Thypars" refers to animals from which both thyroid and parathyroid glands have been removed; "Parathy" indicates parathyroid removal alone.
† Same controls for Thypars and Parathys.

has been noted in an earlier paragraph and the present record serves to substantiate its validity. That no similar reaction is shown in the male is further evidence in support of the belief, to which the pertinent correlation coefficients give additional support.

On Chart 2B the growth response of the hypophysis to parathyroid deficiency in the male is compared with that in the female. The retardation tends to be less in the female than in

the male. This in general is merely an expression of the dependency of the hypophysis on the body as a whole under these conditions, since as was shown in an earlier paper (25), the body weight of the female tends to be less retarded after parathyroid removal than does that of the male.

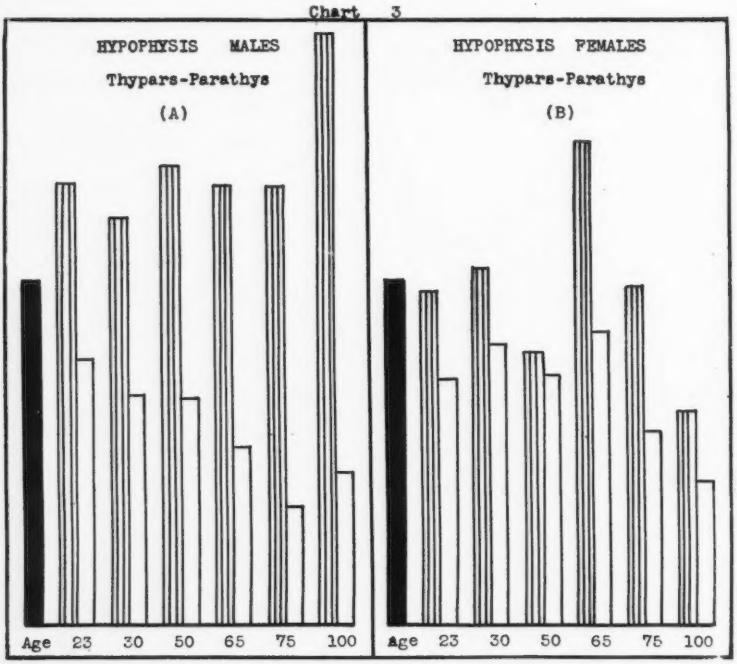

Chart 3. The growth of the hypophysis after thyroid removal compared with that after parathyroid removal. A—Males. B—Females. Order of sequence given by the superscript.

The influence of the two types of glandular deficiency on the growth of the hypophysis in the male and female rats is shown in Chart 3A and B.

It is at once evident that the response of the organ to thyroid deficiency differs both in kind and degree from that produced by parathyroid removal. The difference indicates clearly that the specificity of hypophysis-thyroid relation is not shared by the parathyroids, which is further evidence justifying the

interpretation of the growth results of thyro-parathyroidectomy in terms of thyroid deficiency alone.

SUMMARY AND CONCLUSIONS

A report and an interpretation of the growth relation of the hypophysis to the thyroid apparatus is given.

The data lead to the following conclusions:

1. Thyroid deficiency conditions a consistent hypertrophy of the hypophysis in the male but not in the female.

2. The size and presumably the activity of the hypophysis is specifically related to the activity of the thyroid when this exceeds the usual limits in either direction.

3. This relationship is conditioned by gonadal incretory activity in the female but not in the male.

4. There is no specific growth relation between the hypophysis and the parathyroids.

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REGENERATION OF THE THYROID, AN EXPERIMENTAL STUDY*

J. EARL ELSE, M.D., M.S., F.A.C.S.; HORACE M. GROW, M.D., AND CHARLES W. LEMERY

From the Department of Surgery, University of Oregon Medical School

PORTLAND

Wagner in 1884 first reported hypertrophy of the remaining lobe of the thyroid following lobectomy. Wagner's observation was based upon the appearance of the gland and not upon microscopic examination. He made only two experiments, one upon a dog and one upon a cat. Horsley, in 1886, confirmed Wagner's report and showed that there were both hyperplasia and hypertrophy of the epithelial cells with plication of the walls of the acini. Horsley states that he did not find any increase in the cells of Webber and saw no evidence of metamorphosis of embryonic tissue into acini. Cristiana observed hypertrophy in a small transplant of the thyroid gland when the greater portion of the gland had been removed. Manley and Marine have since reported that if iodine is given to the animals this hypertrophy will not occur.

Halstead's work first reported by Welch in 1888 and later by Halstead in 1896, was more extensive than anything preceding. He established the fact that: 1. Total extirpation of the thyroid gland is followed by an early death; 2. Dogs will survive if at least one-eighteenth of the thyroid substance is left; 3. Puppies from females having had one lobe or more removed, have goiter at birth; 4. Thyroid enlargement may follow infection. Halstead evidently removed the parathyroid for his description of death from total extirpation is very suggestive of parathyroid tetany. All puppies from females which had one lobe or more removed had goiter. There was no goiter in the puppies from females which had not been operated upon. This enlargement should not be regarded as an inherited goiter but rather as a fetal enlargement due to the attempted functioning of the thyroid in utero because of insufficient thyroxin in

* Read at the Tenth Annual meeting of the Association for the Study of Internal Secretions, Dallas, Texas, April 20, 1926.

the mother's blood. From Halstead's paper, apparently the removal of a portion of the thyroid of the male had no effect upon the puppies.

Halstead believed that the hyperplasia occurred in the follicular cells, but in one of his pictures there is a very definite hyperplasia of the interacinar cells of Webber. (Fig. 1.) In describing the blood vessels, he states that they differentiate epithelial cells in what might otherwise be a jumble of interfollicular cells without arrangement, by surrounding primitive follicles, but from his picture and description it would seem

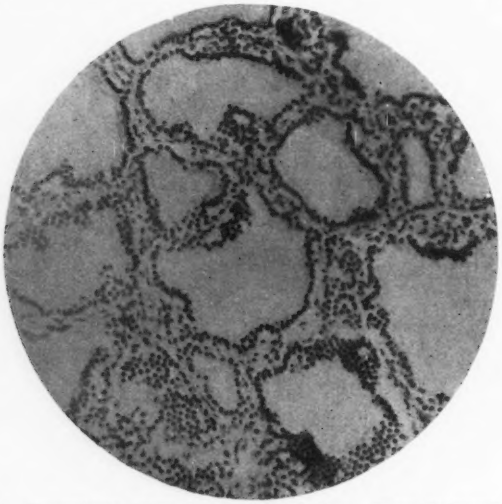

Fig. 1. Hyperplasia interacinar cell of Webber. From Halstead's publication in 1896.

more probable that these were primitive follicles developing as a result of the hyperplasia of the interacinar cells. He also describes definite hyperplasia of the follicular epithelium such as is seen in exophthalmic goiter. This was accompanied by a decreased thinning and vacuolization of the colloid.

Hunnicutt did not obtain the same results as did Halstead. In 59 experiments upon dogs, hyperplasia developed in only three. Marine accounts for the difference between Hunnicutt's and Halstead's work on the basis of the use of iodine as an antiseptic by Hunnicutt but not by Halstead.

Marine, in a paper written in 1907, concludes that hyperplasia of the thyroid is a physiological reaction in a deficient gland and that colloid goiter is usually preceded by a stage of hyperplasia and in its uncomplicated form is to be regarded as a quiescent state of the hyperplastic form. He also showed that the giving of iodine to dogs with the hyperplastic form, resulted in colloid secretion.

Loeb in 1919, in working upon guinea pigs, found that hypertrophy occurred after the greater portion of the gland had been removed. This hypertrophy might appear during the

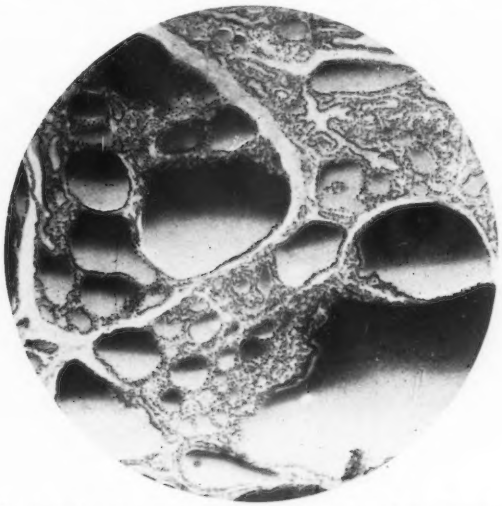

Fig. 2. Colloid goiter (human) with hyperplasia and the formation of acini and definite tubules interacinar.

second week, but usually appeared between 15 and 18 days. Cell multiplication usually ceased at the end of 22 days, but might persist for 30 days. The evidence of hyperplasia persisted for some time and could often be seen in the acini after four or five months. New formation of colloid occurred after six or eight weeks, having at first a viscid characteristic such as is seen in hypertrophied glands. Quantitative relationship was found between the amount of thyroid removed and the amount of hypertrophy, but the same order of change and the same lapse of time occurred regardless of the amount removed. Abor-

tion usually, but not always, followed complete extirpation in pregnant guinea pigs, but did not promote compensatory hypertrophy in either the mother or the fetus.

Crawford and Hartley, in a recent paper in which they studied the effect of lobectomy upon the remaining lobe, found that within two days there was a beginning increase in colloid secretion, which continued to increase until the seventh day, at which time the acini were increased in size, distended with colloid and the epithelial cells were flattened. Following this, com-

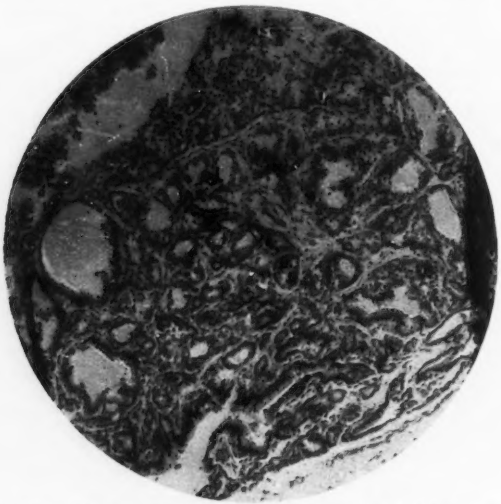

Fig. 3. Hyperplasia with the formation of acini and definite tubules in a colloid goiter of long standing.

pensatory hypertrophy took place. The evidence of compensatory hypertrophy was present after three to four months.

In a previous paper I have traced the development of adenomatosis or diffuse adenomatous type of goiter from the hyperplasia of the interacinar cells, first described by Webber, showing first the development of undifferentiated cells, second the formation of fetal acini, third the beginning of colloid secretion, and fourth the formation of adenomatous masses. In the same paper is shown the development of new acini within old acini from the epithelial cells lining the acini, the process being the same; first the undifferentiated cells, then the fetal acini,

then the beginning colloid secretion, and finally the larger acini containing more colloid.

A study of colloid goiter in the human shows that at first there is an increase in the amount of colloid in the acini. With the distention of the acini the cells become flattened, due partly to a stretching because of the increase of circumference of the acini and partly to increased intraacinar pressure. In patients with a colloid goiter of long standing there is found an increase in the epithelial cells between the acini. At first they present

Fig. 4. Colloid goiter (human) with hyperplasia and new acini formation.

an undifferentiated appearance, sometimes being arranged in a columnar tubular-like structure (Figs. 2 and 3), suggesting the mode of development of the fetal thyroid. This is later followed by the formation of typical fetal acini (Fig. 4), and still later by the secretion of colloid, showing that the acini have taken on physiologic activity. Sometimes new acini are formed within the old acini from the intraacinar cells, as previously mentioned. When this occurs one finds a more or less pyramidal growth within the acini. The more central cells present an undifferentiated appearance; immediately below this is a beginning acinar formation presenting a fetal type of acini; below this the

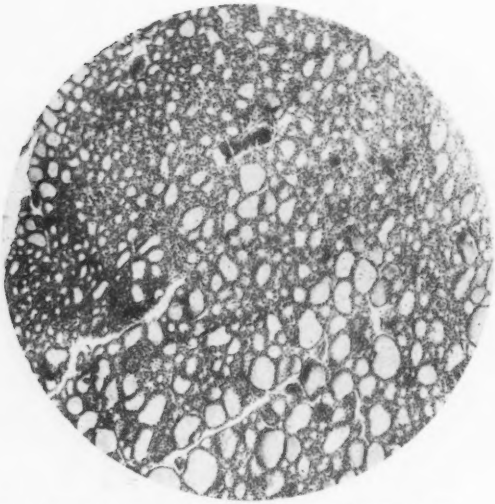

Fig. 5. Normal rabbit thyroid before partial thyroidectomy.

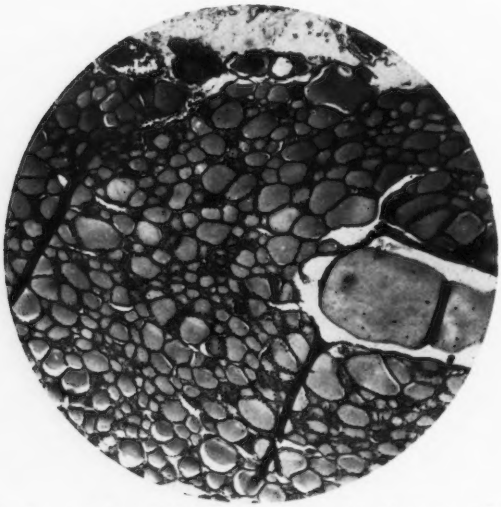

Fig. 6. Increase in colloid following partial thyroidectomy. (Same rabbit as Fig. 5.)

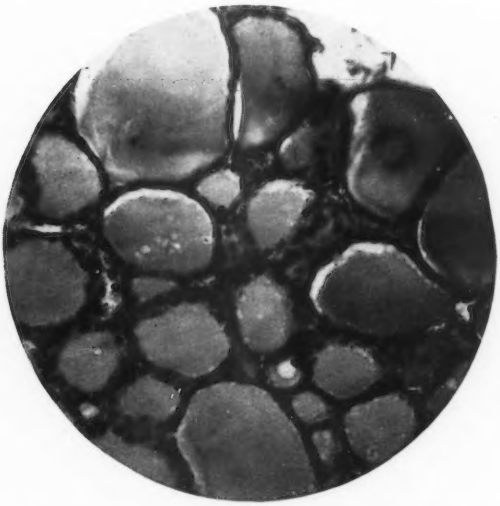

Fig. 7. Hyperplasia cells of Webber in rabbit's thyroid following partial thyroidectomy.

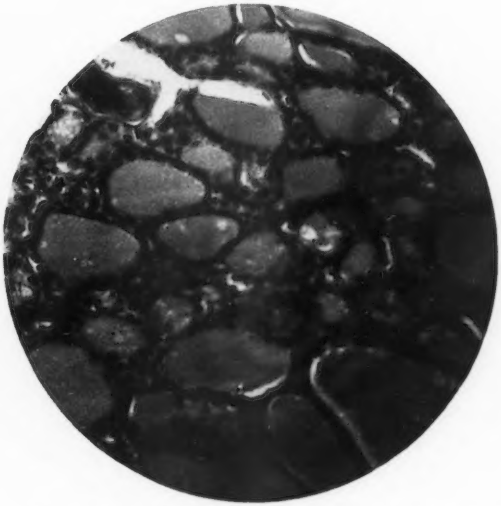

Fig. 8. Hyperplasia interacinar cells of Webber (rabbit) following partial thyroidectomy.

acini show the evidence of colloid secretion, and next to the old acinar wall, definite typical acini are to be found.

In operative work upon goiter it is the custom of most surgeons to remove all but a very small portion of thyroid substance along the posterior portion of the capsule. Many if not all of these patients later have an increase in the amount of thyroid tissue as determined by palpation. In some of them compensatory hyperplasia following the operation continues

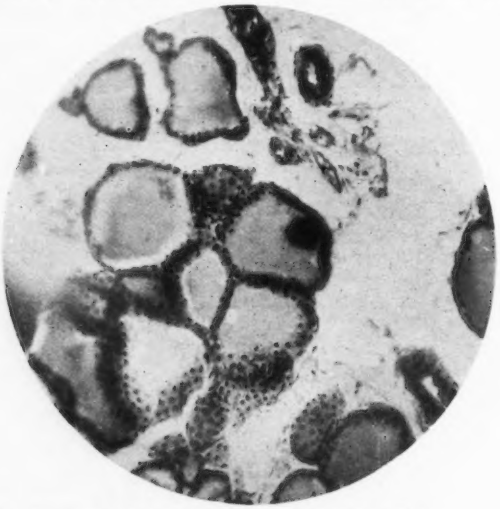

Fig. 9. Formation of new acini within old acini (rabbit).

until another goiter has developed. It was with the purpose of determining, if possible, the mode of regeneration following such operative procedure that experiments have been planned to show the effect upon the thyroid when one-half to three-fourths of the total gland substance has been removed. This paper is based upon that portion of the work which has been completed. A subsequent paper will report the balance of the work.

All of the work has been done upon rabbits. The entire right lobe was removed in all, and in the majority one-half of the left lobe also. The rabbits were permitted to live over periods of time varying from two days to ten weeks. They were then killed and the remaining portion of the thyroid gland was re-

moved and sections were made and compared with those made from the first portion removed. A study of the sections showed that in eight there was no change in the thyroid as the result of the removal of at least one lobe. In four there was an increase in colloid but no other apparent change. In one of these the colloid was vacuolated. In four there was hyperplasia of the interacinar cells (Figs. 7 and 8) with definite formation of fetal acini in one (Fig. 9). In one of these there was hyperplasia in the interacinar cells with the formation of new acini within the old acini in a few places.

In one-half there was practically no change as the result of the partial removal. This we interpret to mean that there was a sufficient amount of thyroid tissue left to meet the needs of the rabbit so that there was no demand thrown upon it for more secretion and, hence, no need of regeneration. In one-half, however, changes were observed, the most common one being an increase in the amount of colloid in the acini. This agrees with the findings of Crawford and Hartley, who state that the first change is an increase in colloid and is at variance with the opinion expressed by Marine that the first change is a hyperplasia. We interpret the findings in this group to mean that with the increased cellular activity a sufficient amount of thyroxin was secreted so that regenerative changes did not occur. In four rabbits there was a definite cellular hyperplasia occurring in the interacinar cells. This was evidenced mainly by an increase in the number of these cells but also in the formation of new acini. In one of these there was seen new acini formation within the old acini.

SUMMARY

In an incomplete series of experiments on sixteen rabbits partial thyroidectomy was performed. It was found that, first, so long as there is a sufficient amount of thyroid gland left to supply the necessary thyroxin to the animal there are no changes in the gland as the result of removal of same; second, that when a sufficient amount of thyroid substance is left so that stimulated activity on the part of the cells can supply enough thyroxin, regeneration will not take place and the increased cellular activity is shown only by an increase in colloid; third, that when there is not enough thyroid left to meet the needs

of the animal, hyperplasia takes place, developing usually from the interacinar cells of Webber, but also from the intraacinar cells, and in each case new acini are formed.

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THE DEVELOPMENT AND NATURE OF THE SO-CALLED TOXIC ADENOMAS*

ARTHUR E. HERTZLER
HALSTEAD, KANS.

The interpretation of the meaning of the changes which take place in the so-called toxic adenomas is much more than of academic importance. If there is a hyperplasia leading to hyperfunction we are justified in the hope that a regression to the normal may take place. If it is a degeneration, then a restitution to the normal is out of the question. That any surgical procedure which leaves part of the diseased organ is not ideal surgery goes without saying. What comes of the part remaining after operation is not known. All surgeons frankly admit that cures are not complete in a certain proportion of cases. What ultimately becomes of the cured cases only the future can tell. Why some are not cured is a matter of immediate concern. What proportion of the "cured" ones remain well is still a matter of speculation, for we know that some patients remain symptom-free for a number of years and then they are sick again. Little thought has been given to this class of cases. These problems make it quite likely that new viewpoints are needed before we can advance much in the surgical management of goiters.

The first lap in the study of this problem is to determine the meaning of the degenerative changes which take place in colloid goiters, and the factors active in the production of the toxic manifestations. There is much talk about the active and resting stages, the regression to normal and the like. Much of this is based on speculation. Those who have experimented with the resection of goiters know how confusing the results are. One experimenter finds there is a hyperplasia of the remainder of the gland. Another finds that hyperplasia does not take place—and explains the divergence of results on the ground that the animal's neck was painted with iodine. Such attempts to force the results of experiments into harmony is enough to make the judicious grieve. Viewed broadly, one is compelled

* Presented at the Tenth Annual Scientific Meeting of the Association for the Study of Internal Secretions, Dallas, Texas, April 20, 1926.

to admit that experimentation on animals has as yet not succeeded in permitting the deduction of any general laws. Clinical evidence is still the most fruitful source of information in determining what happens in the human being.

We are greatly in need of records of studies of the parts of glands remaining years after the removal of the most of the gland. Autopsies in such cases are greatly needed. There is accumulating evidence that, in many, a state of myxedema is approached and is preferable to the presence of part of a crippled gland. Some of my myxedematous patients have been under observation 30 years and more and are living in perfect health and contentment. So impressive are such cases that one must ask himself whether or not a grain a day of bouvine thyroid is not a better protection against senility than a dependence on our own aging thyroids. At least it is safe to assert that a surgical myxedema is not a calamity to be feared, when we face the severer forms of thyroid gland malfunction.

Working with goiters it is necessary sometimes to stop and inquire if we are working with symbols or real facts. The things we know for certain are few. The one certain thing is that myxedema is relieved by the constant use of thyroid extract. Nearly as certain is it that a typical case of exophthalmic goiter is associated with proliferation of the epithelium of the acini. Quite constant is the relation of the "toxic adenomas" to long existing goiter. From the purely surgical standpoint we know nothing as to etiology. The exophthalmic type is believed to be more or less a constitutional condition with local manifestations in the thyroid gland. To this surgery has to answer that when Basedow patients are operated on early and as completely as the surgeon dares, keeping in mind only the recurrent nerves and the parathyroids, the results are complete and permanent. This makes it appear that the real seat of the trouble lies in the thyroid after all. Long existant exophthalmic cases are associated with all sorts of general symptoms which are not wholly relieved by operation. Once an exophthalmic patient has undergone a remission irremovable complications may appear. These are looked on as primary and the goiter as secondary, but this is erroneous in the light of the results of early, bold surgical treatment.

It is of interest to inquire whether the injury is done by the imperfect colloid which forms during the height of the disease, or if it is done by the hypersecretion of the epithelial cells. Those that have degenerated areas are the ones which do not give good results after operation.

If we look at the life history of the so-called toxic adenoma we learn that it is generally agreed that a long period of time elapses from the beginning of the goiter to the beginning of serious general symptoms—a state which we symbolize by the word "toxic." This period may be stated in round numbers as sixteen years. This period is dated from the time the patient first becomes aware of the presence of the goiter, which means that at that time the goiter was already of considerable size. As to when the increase in size of the goiter actually began there is little evidence. What the goiter was doing during the years of its "innocent" adolescence has not been sufficiently scrutinized. Worse still, most writers seem to imply that the goiter exerts its baneful influence with a certain degree of suddenness. Observation of these colloid goiters through the decades convinces me that there is nothing sudden about it. The various symptoms are in evidence years before the patient is aware of it. I imagine that the fabled camel complained that some guy dropped a load of straw on his back causing a fracture of the vertebrae. Now if he had been observant he would have known that the accretion of straw was gradual and all save the last straw was innocent of harm. It would be safe to say to a camel accumulating a like load that if he does not stop the procedure somebody is going to drop on one straw too many. So we can say to patients with the old colloids, "If you don't get rid of it, it will get you sometime."

I have been feeling goiters and sectioning goiters in this community more than 30 years. This experience convinces me that an attempt to distinguish between adolescent, the slightly toxic and the multilobular colloids is no more sane than attempting to classify the separate weeks in typhoid fever as separate diseases.

I can multiply such pictures as the following: A young girl has an enlarged gland, a perfectly innocent thing, and will disappear (30 years ago). That the girl was nervous and had dysmenorrhoea was unfortunate (30 years ago child birth would

relieve this; 20 years ago the Battie operation; 10 years ago dilatation, currettage, the stem pessary or the removal of a "chronic appendix"). But the goiter was innocent. With the passing of years and the advent of pregnancy the goiter reappeared, uniform in outline, soft or elastic in consistency, otherwise innocent. Intimate acquaintances noted the patient was more irritable than formerly but she being possessed by (or with) a husband and children, who needs to look to the thyroid as a cause of nervousness? The goiter shows an irregularity here and there and in time becomes lobulated. It is now a lobulated colloid. Sometime between 34 and 55 the patient notices some shortness of breath, irritability, loss of weight and perhaps more serious symptoms. But there are the children in society and the enlarging prostate all calculated to disturb mother's rest (thus we thought 30 years ago). These symptoms increased and anorexia supervened, rapid emaciation and mother was buried, innocent goiter and all, now these thirty years ago.

We now know that the demise of the hypothetical case was caused by a toxic adenoma. But we are as ignorant as ever as to the actual cause of death. Symbolized complacent ignorance.

The only means we have of charting the course of such cases is to examine a large number of goiters removed from patients representing the various stages of the disease and correlate them with the clinical symptoms.

Histologically we have in the early stages a goiter which shows an increase in the colloid. The acinal epithelium shows but little change. Those associated with nervous symptoms (and usually dysmenorrhoea) we find some degeneration of the colloid, some flattening of the acinal epithelium and some increased prominence of the interacinal cells. During the long, innocent stage when the gland is becoming nodulated a most varied picture is encountered. The one constant thing is that acinal cells are flat and obiously inactive. New glands form in the interacinal cells. These, too, have flat cells, obviously inactive. The colloid is degenerated. The connective tissue is increased in amount and has undergone various types of degeneration. Epithelial cells are found in groups in masses of degenerated connective tissue. Such cells certainly are not capable of performing any function. Such pictures as these are found in the

old innocent goiter and the toxic adenomas. There is no sharply dividing line.

It has been assumed that it is the gland proliferation which is responsible for the constitutional symptoms. This is pure assumption. Against this assumption is the very pertinent fact that these are harmed by iodine while the cell-active type (the "Basedows") are helped by this drug. It is not explained how this could be if both types owe their activity to an increase of the acinal epithelium.

It must always be remembered in this connection that a true "Basedow" may be implanted on an old colloid goiter. The clinical findings and the history should enable one to determine with a considerable degree of accuracy which are the combined cases. The histology shows such combinations clearly. This becomes more obvious when the course of the disease after operation is compared with the slide from time to time, for neither our interpretation of the slide nor our judgment of the clinical conditions is infallible.

The important fact in this connection is that the whole gland of the toxic adenoma is diseased. The histology indicates that it is injured beyond repair. According to present methods we remove a part of the diseased tissue. This is unsurgical. The demands of ideal surgery dictate that the whole of the diseased tissue shall be removed. The question is, are we able at this time to meet the ideals in the surgical treatment? The result is a myxedema. This myxedema can be controlled by the use of thyroid extract. There are no more comfortable persons than those myxedemics who take their grain a day. This is better than to allow the patient to depend on the remaining part of a hopelessly crippled gland. I believe the facts will substantiate this statement. We need more detailed knowledge, both in pathology and clinical diagnosis, before we can speak with assurance. Besides, the technical difficulties in removing all the gland are by no means small. Something more exact than the grab and cut method commonly employed in thyroidectomy must be adopted. The recurrent nerves and the parathyroids must be spared.

Much work must yet be done in which the whole gland is deliberately removed. The production of myxedema is still considered an actionable offense, and no one cares to publish evi-

dence for the use of the attorneys for the plaintiff. The law requires the surgeon to exercise the skill common to the profession in his environment. To do better than the average is as great an offense as to do worse.

GOITER: CURRENT ERRORS IN ETIOLOGY AND TREATMENT

ISRAEL BRAM, M.D.
From the Bram Goiter Institute
PHILADELPHIA

A goiter is not merely a lump on the neck, but a local expression of causes originating or having originated elsewhere in the body. Also, contrary to popular notion, the cure of goiter is not necessarily by means of iodine or by thyroidectomy. In a prolonged study of the subject, with a series of thousands of cases, I have found that a large percentage of patients seen have already been iodized, thyroidectomized, or both, with detriment to the individual.

The reason why treatment of goiter is still largely chaotic is that the doctor's span of existence is too short to know everything about everything in medicine. The subject of goiter, because of its broad implications with regard to pathogenesis and subjective and objective symptomatology, frequently requires a most widespread regime of therapeusis. Goiter is a specialty and is as large and exacting as any in medicine. Even the few goiter specialists to be found in this country have still very much to learn on this subject. Each day presents new problems requiring solution.

There are several common misconceptions on the goiter question.

That we can dispense with the major portion of the thyroid gland is a fallacy employed daily by thyroidectomists who do not differentiate between surgical and non-surgical goiters. An encapsulated, truly neoplastic goiter must be removed in such manner as best befits the case in hand, and a careful thyroidectomy is the only treatment acceptable.

On the other hand, *simple hypertrophy* and *colloid goiters* indicate the need for *more* thyroid secretion, and the basal metabolism in these patients indicates a tendency toward hypothyroidism. Such goiters should be treated not by surgery, but by the elimination of discoverable causal factors, and, if necessary, the cautious administration of thyroid hormone to rest

the organ. *Puberty hyperplasia* is a status in which the individual presents a strong susceptibility to Graves' syndrome. Here, too, casual relationships should be sought and the proper corrective measures instituted by an internist. In *exophthalmic goiter* (Graves' syndrome) nature resents thyroidectomy as evidenced not only by the high operative mortality rate (statistics notwithstanding), and lack of clinical cure, but by return of the goiter. It is here especially that surgeons claim the need for the removal of three-fourths, five-sixths, seven-eighths, and recently even the entire thyroid gland! This latter procedure has just been advocated by Gilman and Kay.*

If, as Crile says, the thyroid is what makes life worth living, then life is worth living only in proportion to the amount of normal thyroid structure possessed by the individual. The hyperplastic thyroid may be compared to a loaded sponge which unloads itself, shrinking to its former normal size and structure following properly applied non-operative measures *not necessarily directed to the thyroid itself.* If we could follow in our mind's eye the physiological variations of thyroid activity, we should see this organ's function waxing and waning with the mental and physical actions of the person's daily life. In order successfully to cope with problems in the fight for self-preservation and the strife incident to the march of civilization, one must possess sufficient thyroid structure and function during physiological stress and strain. Without it we fall by the wayside. How can the surgeon reconcile himself to these facts and at the same time claim that an individual can "get along" with a tiny fraction of the amount of thyroid endowed him or no thyroid at all? Such an attitude is an assumption on the part of the thyroidectomist that he knows more about the mystery of life's processes than does nature herself. The fact remains that sooner or later those who have been considerably or completely thyroidectomized become a burden to themselves and society. Even sheep's thyroid is incapable of satisfactorily substituting entirely for the human hormone.

That goiter is necessarily a disease of the thyroid gland is not true. It, therefore, must not be treated as a local condition. With few exceptions, all goiters begin as local expressions of

* Gilman, P. K. & Kay, W. E.: Total thyroidectomy in thyrotoxicosis of the exophthalmic type. Am. J. M. Sc. (Phila.), 1926, 171, 239-245.

disturbances elsewhere in the economy. In regions away from goiter belts simple hypertrophy and colloid goiter are usually due not to lack of iodine, but to the premenstrual status, adolescence, pregnancy, heredity, focal and general infections, intestinal intoxication, pelvic neoplasms, and other conditions away from the thyroid gland. Untreated, thyroid swellings of this sort occasionally disappear spontaneously. Most often, however, they persist, and in the course of time pathological changes within the thyroid may so change the mass as to give rise to adenomata or cysts. Thus we now have a kind of local condition requiring thyroidectomy even though the primary cause may have disappeared. Originally, however, the goiter was not a disease of the thyroid, requiring not local attention, but a correction of the underlying causal factors.

That there are two kinds of goiter, simple and toxic, is another common misconception. Goiter may be toxic, giving rise to thyrotoxemia when in a state of hyper-secretion, but there is no such thing as a "simple" goiter. Rather than "simple," we might use the term non-toxic in contradistinction to toxic goiter. A non-toxic goiter, though not secreting an excess of thyroid, is a rather complicated affair, as mentioned in the preceding paragraph.

That all toxic goiters are cases of hyperthyroidism is not true. There are four types of toxic goiter: (a) toxic adenoma, synonymous with hyperthyroidism; (b) puberty hyperplasia, synonymous with the pre-Graves' disease status; (c) diffuse adenomatosis, an uncommon condition about which more will be known in the future; and (d) exophthalmic goiter, synonymous with Graves' disease, Basedow's disease, Parry's disease, Flajani's disease, dysthyroidism, etc. Exophthalmic goiter is not, and is not due to, hyperthyroidism. A realization of this fact would put an end to much irrational therapeusis.

That basal metabolic tests are infallible is an error usually entertained by the enthusiastic laboratory man who has not sufficient opportunity to observe the human being under the stress and strain of thyroid dysfunction or of Graves' disease. Calorimetry is one of the most valuable laboratory aids. On the other hand, to depend upon it alone for diagnosis, as is frequently done, is a mistake. Rather would I trust the trained senses in the diagnosis of the presence and severity of hyper-

thyroidism, than a mere brainless instrument, the sources of error in the manipulation of which are numerous enough to fill a good-sized monograph.

I find basal metabolic determinations useful for *diagnostic* purposes in merely 5 per cent of cases. Calorimetry is useful in the determination of the *progress* of the patient under treatment in approximately 50 per cent of cases. The greatest value of basal metabolic determinations properly performed under ideal conditions lies in *confirmation of recovery.* Strictly speaking, the trained senses of the well equipped goiter specialist are sufficient to determine recovery; but there is an indescribable sense of ease and pride in knowing that basal metabolic determinations *confirm* the findings through the expert use of our senses.

That all goiters require surgery is an error that leads to unnecessary thyroidectomies and destruction of confidence of the laity in the medical profession. The *therapeutic classification* of goiter is the safest guide. This divides goiter into two classes: (a) Surgical goiter, requiring thyroidectomy; among these are such encapsulated neoplasms as adenomata and cysts; thyroid enlargements substernally or intrathoracically located or those of such size as to occasion marked pressure symptoms, likewise require surgery. (b) Non-surgical goiter, consisting of unencapsulated thyroid swellings such as simple hypertrophy, colloid goiter, puberty hyperplasia, and the hyperplastic thyroid of exophthalmic goiter or Graves' disease. These four types of thyroid swelling yield splendidly to a properly applied regime of non-operative therapy, and when erroneously thyroidectomized, not only present recurrence, but sequential constitutional derangement as well.

That all rapid hearts in association with goiter are due to thyrotoxemia is likewise not true. Tachycardia, in the presence of goiter, is usually due to the latter, but exceptions to this rule are numerous. (a) The patient may have paroxysmal tachycardia, or an organic heart lesion totally independent of the thyroid enlargement, the goiter occurring merely as an incident. (b) The subject of goiter may be suffering with a febrile condition accounting for the rapid heart action. (c) Extremely sensitive, apprehensive, or self-conscious patients who, under ordinary conditions have a perfectly normal heart rate, applying

to the physician for the treatment of an innocent goiter, may present such a flare-up of the heart rate as to give rise to the opinion on the part of the examiner that he is dealing with a case of "toxic" goiter. (d) An otherwise harmless thyroid enlargement but substernally or intrathoracically located, may give rise to so-called "mechanical goiter heart," due to circulatory and respiratory mechanical embarrassment because of the aberrant location of the mass. This latter status is most often confused with the "thyrotoxic goiter heart," the term applied to a heart under the influence of a hyperactive thyroid.

That the medical treatment of goiter consists in the administration of iodine is a fallacy responsible for more goiters than have ever been seen before. The use of iodine in the prophylaxis of goiter in endemic districts may be a useful procedure, though no doubt many persons receiving iodine in goiter belts are not susceptible to goiter and are therefore being unnecessarily drugged. Doubtless a fair percentage of small goiters occurring in goiter belts are due to a deficiency of iodine in air, food, or water, hence are curable by iodine therapy. Here, too, it must be remembered that goiters seen in endemic districts are not necessarily endemic goiters, but may be due to sporadic causes not dependent upon iodine deficiency.

The protagonists of iodine therapy in the management of goiter have committeed a great error of omission. They omitted to qualify their statements and point out that iodine is only to be employed where it is reasonably certain that the patient is suffering from iodine deficiency. The *universal* administration of iodine, with its propaganda favoring the use of this drug indiscriminately, is a menace to the health of the community. Iodine is a potent drug, to be given only upon the advice of a competent physician—a medical man who is capable of passing judgment upon the needs of thyroid patients. Indiscriminate administration of iodine, coupled with self-drugging by many persons who purchase iodine or its proprietary compounds with a view to curing goiter, has been responsible for the growth of almost invisible thyroid enlargements into large, bulky goiters, and what is worse, simple, non-toxic goiters become those hypersecreting masses that bring about marked circulatory and nervous deterioration. The medical profession is beginning to awaken to this danger, and the sooner there is a concerted ac-

tion against this iodine propaganda and its legislative enactments, the better it will be for the American public.

That exophthalmic goiter is the proper term for the syndrome observed leads to erroneous diagnostic, clinical, and therapeutic implications, and hinders progress. A goodly percentage of sufferers from this disease present neither exophthalmos nor goiter, yet are suffering with the affection. To depend upon exophthalmos and goiter for diagnosis is harmful to the patient, as diagnosis is often unduly postponed and the appropriate treatment applied too late. Moreover, since goiter, when present, is merely an incident in this widespread syndrome, the disease being largely characterized not by hyperthyroidism but by nervous, emotional, circulatory, gastrointestinal, cutaneous and other evidences of a generalized neuro-endocrine imbalance, this disease should not be regarded as belonging in the category of goiter, but should be looked upon as a *constitutional* affection. Goiter is no more a primary element in the etiology and symptomatology of Graves' syndrome than is the enlarged spleen that of typhoid fever. Each is a secondary element, a defensive reaction in a generalized condition. Hence the term exophthalmic goiter should be discarded and the term Graves' disease employed for want of a better name.

That the "medical" treatment of exophthalmic goiter consists of the administration of a drug such as iodine or quinine, is a notion on the part of both internists and surgeons that gives rise to the entire difficulty with the therapeusis of Graves' disease. The internist, failing to cure his patient by the administration of a drug, concludes that "medical" treatment is a failure, and turns the sufferer over to the surgeon for thyroidectomy. The surgeon, recognizing the failure of "medical" treatment, proceeds to operate. But eventually, surgery having failed to produce cure, he attributes this failure to lack of "subtotality" of thyroidectomy, and another operation is performed. Indeed, 30 per cent of sufferers with Graves' disease sent to me for consultation already present one or more scars of thyroidectomy, and are in worse plight than ever before.

The "medical" treatment of exophthalmic goiter should give way to what had best be termed the *nonsurgical management of Graves' disease.* This does not consist of the administration of a drug. It presupposes that the medical attendant

is thoroughly equipped to manage a patient of this type. The keynote to success in therapeutic management is strict individualization, with the administration of such measures as qualified rest, diet, medicaments, occasionally electricity, and psychotherapy permeating treatment in all directions. Having eliminated all discoverable causes, these measures are employed in suitable quality and quantity by the properly experienced internist for the proper length of time. In the event of unequivocal co-operation on the part of patient and household, complete, permanent recovery occurs within from six to twelve or fourteen months, the duration depending upon the chronicity and severity of the syndrome. Such a patient, taught how to eat, how to sleep, how to rest, how to work, and even how to think, is permanently restored to usefulness and happiness, and enjoys unprecedented health.

We cannot overestimate the the importance of this topic. If we consider the vast number of goiter cases in our midst—at least 5,000,000 in this country—we cannot but hope that there will soon be a clarification of this enormous problem for both the medical profession and the lay public.

PRESENT STATUS OF THE PROBLEM ON TRYPTOPHAN AND THE THYROID GLAND

HSI CHUN CHANG

From the Hull Physiological Laboratory of the University of Chicago

The hypothesis that "tryptophan is the mother substance of the thyroid hormone" (Cramer, 1923,), were it true, would be very significant. Physiologically, it would settle the complex problem as to the origin, genesis, and the nature of the thyroid hormone; and clinically it would justify the trial use of tryptophan deficient diet in the treatment of exophthalmic goiter (Harries, 1923). During the last two years evidences pro or con have accumulated. This paper summarizes all facts available in order to point out where this important question stands today.

HISTOLOGICAL EVIDENCE

This has been studied independently and almost simultaneously by three groups of workers, all using the albino rat as the experimental animal. Their findings are more or less the same, but their interpretations are by no means in harmony with one another.

Cramer (1923) finds that rats on a diet rich in vitamin but poor in tryptophan develop "a very characteristic atrophy of the thyroid gland," which "does not occur in vitamin B deficiency." From this finding alone he concludes that "tryptophan is the mother substance of the thyroid hormone."

Chang (1925) confirmed Cramer's finding of atrophy in the thyroids of rats on tryptophan-deficient diet, but found similar thyroid atrophy in animals of parallel state of malnutrition brought about by restricted amount of *adequate* diet. Moreover, he was unable to demonstrate any change in the thyroids after daily subcutaneous injection of excessive amounts of tryptophan for a long period of time. Furthermore, when a heavier animal was put on tryptophan-deficient diet, and sufficient amount of tryptophan was given to maintain the body weight so that at the end of the experiment it was considerably heavier than its pathological controls, i. e., animals on chronic starvation and tryptophan-deficient diet alone, the thyroid was found

to be the nearest to normal structure of the three. On the other hand, where the final body weight of the tryptophan injected animal fell to the same level as those of its pathological controls, the thyroid was as atrophic as those of the other two in spite of the tryptophan given. He is, therefore, inclined to think that the thyroid atrophy in animals on tryptophan-deficient diets, as has been described by Cramer, seems to be due to the disturbed nutrition of the animal rather than the absence of a specific influence of tryptophan on the thyroid gland.

Abel, Bachus, Bourquin and Gerard (1925) report two coexisting findings in the thyroids of rats fed on tryptophan-deficient diet. In the first place, "the thyroid appears so nearly normal that it seems to obtain the amino acid from the blood plasma at the expense of other tissues, to the end to produce its secretion." In the second place, "it did exhibit a definite increased cellularity consistent with moderate strain," and "if this strain is long continued and severe," thyroid atrophy as described by Cramer follows. Their conclusion, therefore, agrees with Cramer, but the two different explanations based on two different findings of a same thyroid gland seem to be more improbable than contradictory.

The recent cytological work of Chang in collaboration with Dr. Wen Chao Ma, to be reported later, has corroborated his former findings satisfactorily.

At present we believe that the histological evidence from which this far-fetching hypothesis has been derived is untenable.

PHYSIOLOGICAL EVIDENCE

McCarrison (1924) claims that tryptophan, leading other amino acids studied, retards the metamorphosis of tadpoles, increases the colloid secretion of the thyroid and induces "ill-developed if not actually atrophic thyroids" among the smallest tadpoles. The size of the thyroid is increased with large vesicles by tryptophan, but decreased by other amino acids tested. The interpretation of these findings is not given.

The retardation of tadpoles' metamorphosis is not significant in terms of thyroid function, because Gudernatsch's phenomenon seems to be a test for some non-specific iodine compounds (Swingle, 1918, 1919, 1922, 1923, 1924). It is interesting to note here that the amino acids, for whatever reason

it may be, have a general reaction towards retardation of the tadpole's metamorphosis, which in turn might be responsible for the changes of the thyroid gland described.

CHEMICAL EVIDENCE

Weir (1925) has assayed 52 glands of exophthalmic goiter and adenomatous goiter, and has found that the average tryptophan content is approximately 3%, being higher than that of casein; but there is no definite relationship between this tryptophan content and the pathological type of the gland or the thyroxin content or the basal metabolic rate.

Most of the evidences to date are not in favor of the assumed importance of tryptophan in the thyroid gland function. Further physiological and chemical evidences are necessary to decide this question.

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STANDARDIZATION OF PREPARATIONS OF OVARIAN FOLLICULAR HORMONE

E. P. BUGBEE AND A. E. SIMOND

From the Medical Research Laboratories of Parke, Davis & Company
DETROIT

Allen and Doisy and their associates (1) in 1924 originated the "*rat unit*" as the standard by which the potency of preparations made from ovarian follicular fluid are measured. Their definition is as follows:

"Provisionally we wish to define a *rat unit* as the quantity of material necessary to induce estrus as judged by the smear method in an ovariectomized sexually mature rat weighing 140, plus or minus 20 grams. For physiological reasons we generally make three injections at intervals of 4 hours. The *rat unit* then is the minimum amount so injected which produces full estrus growth in the genital tract. Although we are convinced that this method of testing is roughly quantitative, we have not yet made a careful study of its limitations."

This *rat unit* as defined above is used as the standard of potency for preparations of ovarian follicular fluid made in this laboratory. Potency is expressed in number of *rat units per cc.*

In making use of the *rat unit* as a practical standard it very soon became apparent that it was necessary to know whether or not the minimal dose which would cause oestrus in a spayed rat varies directly with the weight of the rat. It was difficult to keep a large number of spayed rats of about 140 grams weight. Rats normally weigh 140 grams when about 3 months of age and grow so rapidly that in another month some of them weigh over 200 grams.

In this laboratory we have worked for several months on this problem. We have used rats from one month up to 12 months of age in order to learn if the age of the rat had a direct influence on the effectiveness of the ovarian follicular hormone. In normal rats one month of age injections of small doses of active follicular fluid extracts caused opening of the vaginal orifice and thickening of the vaginal mucosa, and cells obtained

from the vagina showed the forms characteristic of oestrus. As oestrus in such young animals is not physiological it did not seem advisable to use them in standardization. Female rats usually reach sexual maturity, as evidenced by the opening of the vaginal orifice, when two to four months of age. For practical standardization it is important to know that the female rats have normal reproductive organs and this opening of the vaginal orifice is the earliest indication of such normality. In the older age groups we have kept rats under examination for two weeks during which time vaginal smears were taken daily. Only rats were used which showed regular oestrous cycles.

In order to keep rats in a normal condition it is very essential that they be well taken care of. They are very sensitive to changes of temperature, so should be kept where the temperature is constant. They must not be crowded too closely together. In this laboratory only six or eight are kept in cages 21x15x12 inches. Rats will not have regular oestrous cycles unless they are given an adequate amount of food containing sufficient vitamins A and B. For our purposes we have found the Sherman ration (2) satisfactory. This has a great advantage over many other standard rations in that it is so easily prepared. It consists of whole wheat flour 65 per cent, whole milk powder 33 per cent, and sodium chloride 2 per cent of the weight of the flour.

Normal mature female rats when not pregnant and not lactating go through regular oestrous cycles so that oestrus occurs every four to eight days. After both ovaries have been removed the rats remain constantly in the resting stage, anoestrus. The operation of removing the ovaries is done under ether anesthesia. Either a single central abdominal incision or two lateral incisions may be made. It is not necessary to ligate the ovarian blood vessels. The incisions are closed by suturing in two layers with fine silk. The lateral incision method has the advantages that incisions less than one centimeter long may be used and the intestines do not have to be manipulated so much. Rats recover quickly from the operation and may be used in experiments in one week. In this laboratory smears are taken from all spayed rats each day so as to make sure that the rats are not having oestrous cycles without treatment. In the scores which have been operated in this laboratory there

have been two rats which began to have oestrous cycles several weeks after operation, showing that the ovaries had not been completely removed and regeneration had taken place.

In order to determine the oestrous cycles in the rats small moist cotton swabs are inserted gently into the vaginas. Glass slides are smeared with these cotton swabs. The cell forms are differentiated by staining with haematoxylin and eosin. (Mayer's haemalum and .5% aqueous solution of eosin.)

According to Long and Evans (3) the five stages of the oestrous cycle are characterized as follows:

Stage I—Pro-oestrus. Before heat begins. No sexual excitement. Vaginal smears show small epithelial cells with nuclei. No leucocytes.

Stage II—Oestrus. The heat period. Copulation accepted. Vaginal smears show large squamous cells without nuclei. No leucocytes.

Stage III—Late Oestrus. The heat period is over. No sexual excitement. Vaginal smears are thick and cheesy, containing clumps of large squamous cells without nuclei. Late in this stage there may be some large epithelial cells with nuclei. There are no leucocytes.

Stage IV—Metoestrus or Postoestrus. The stage of degeneration and leucocytosis. Vaginal smears show moderate numbers of polymorphonuclear leucocytes, squamous cells and large epithelial cells.

Stage V—Anoestrus or Dioestrous Pause. The resting stage. Vaginal smears show polymorphonuclear leucocytes as the predominating cells and moderate numbers of large epithelial cells and strings of mucus.

In this laboratory a reaction to injections is called *typical oestrus* if a smear shows the squamous cells of stage II without a single leucocyte being found. If even one or two leucocytes are found in the stage II smear the reaction is called *atypical oestrus* and it is considered that an insufficient quantity of the hormone was injected.

Allen and Doisy (4 and 1) developed a practical method of obtaining an active extract from the follicular fluid. They precipitate the proteins with alcohol and dissolve and purify the active fraction in ether, acetone and other lipoid solvents. Their final product is a heavy, oily substance which they dis-

solve in corn oil. In our laboratory this method has been modified, so as to be applicable to quantity production, by Messrs. Adrian Thomas and F. H. Tendick. As oils are not readily absorbed when injected subcutaneously they have supplied it in the form of an aqueous colloid solution of the emulsoid type, which is readily absorbed after subcutaneous injection.

The preparation used in the experiment reported in this paper is of such concentration that each cubic centimeter represents the activity of 6 cc. of fresh follicular fluid, obtained from hog ovaries. The potency per liter of the fresh fluid is 1250 *rat units,* which is within the range which Allen and Doisy (1) have reported as the potency obtained by them in their extracts.

Allen and Doisy (1) recommended giving three injections of their oil solution at four-hour intervals when standardizing preparations on rats. As our aqueous solution is absorbed so readily it was deemed advisable to spread the dosage out over a longer period. After considerable experimentation we decided that our preparation gave the best results in rats when given in eight separate injections, four each day on two successive days. When the tests are made according to our method oestrus often occurs on the fourth day of the experiment. Often typical oestrus cell forms, with no leucocytes present, are found in the vaginal smears for only a few hours. For that reason we take several smears at intervals as follows: one on the first day of injection, one on the second day, three on the third day, and three on the fourth day.

Table I gives the data of one experiment which was made to determine whether or not the effectiveness of the ovarian follicular hormone varies with the age of the rats and whether or not the dosage to be used should vary directly as the body weight of the rats.

Throughout the experiment a single preparation has been used and it apparently did not deteriorate during the period. It was put into ampoules and sterilized in the autoclave. The solution was diluted with seven parts of water just before being used. Dosages are expressed in terms of cubic centimeters of the preparation before dilution.

Column 7 gives the number of *rats per cc.* In computing these values the weight of the rats is not taken into account.

Only the value for the smallest effective dose for each individual rat is given.

These values are obtained by using the formula:

$$\textit{Rats per cc.} = \frac{1}{Q}$$

Q represents the minimum number of cc. of follicular fluid extract which will cause typical oestrus in the rat.

Column 8 gives the number of *rat units per cc.* based on the 140 gram rat as the standard. This assumes that the effective dose should vary directly as the body weight. These values are computed by the use of the following formula:

$$\textit{Rat units per cc.} = \frac{1}{Q \times \frac{140}{W}} = \frac{1}{Q} \times \frac{W}{140} = \frac{W}{140\,Q}$$

W represents the weight of the rat in grams. Q represents the minimal number of cubic centimeters of follicular fluid extract which will cause typical oestrus in the rat.

TABLE I

Rats Two to Three Months Old

Rat	Date	Weight	Dose cc.	cc. per Kg.	Result	Rats per cc.	Units per cc.
226	Feb. 9	....	....	....			
	15	112	.3	2.68	Typical oestrus.....		
	23	126	.175	1.39	Typical oestrus.....		
	Mar. 3	142	.25	1.76	Typical oestrus.....		
	9	150	.15	1.00	Typical oestrus.....	6.67	7.15
229	Feb. 9	....	....	....			
	15	134	.25	1.87	Atypical.....		
	23	150	.2	1.33	Typical.....	5.00	5.35
	Mar. 3	162	.225	1.39	Typical.....		
	9	168	.15	.89	Atypical.....		
230	Feb. 9	....	....	....			
	15	128	.2	1.56	Atypical (almost no effect).....		
	23	146	.225	1.54	Typical.....		
	Mar. 3	158	.2	1.27	Typical.....	5.00	5.65
	9	168	.15	.89	Atypical.....		
231	Feb. 9	....	....	....			
	15	118	.15	1.27	No effect.....		
	23	128	.25	1.95	Typical.....		
	Mar. 3	142	.175	1.23	Typical.....		
	9	146	.15	1.03	Typical.....	6.67	6.95
232	Feb. 9	....	....	....			
	15	102	.1	.98	No effect.....		
	23	110	.3	2.72	Typical.....		
	Mar. 3	118	.15	1.27	Typical.....		
	9	120	.125	1.04	Typical (Short).....	8.00	6.85
	Optimum		.125	1.00		8.00	7.15

Rats Three to Four Months Old

Rat	Date	Weight	Dose CC.	CC. Per Kg.	Result	Rats Per CC.	Units Per CC.
251	Feb. 9	140	.1	.72	No effect		
	15	144	.2	1.39	No effect		
	23	162	.175	1.08	Typical ?		
	Mar. 3	172	.25	1.45	Typical		
	9	178	.225	1.26	Typical	4.45	5.65
252	Feb. 9	148	.2	1.35	Typical		
	15	142	.175	1.23	No effect		
	23	162	.2	1.23	Typical		
	Mar. 3	172	.225	1.30	Typical		
	9	184	.175	.95	Typical	5.72	7.5
253	Feb. 9	144	.3	2.08	Typical		
	15	150	.15	1.00	No effect		
	23	166	.225	1.35	Typical		
	Mar. 3	176	.2	1.14	Typical (Short)		
	9	184	.175	.95	Typical	5.72	7.5
255	Feb. 9	152	.4	2.63	Typical		
	15	160	.125	.78	No effect		
	23	182	.25	1.37	Typical		
	Mar. 3	192	.175	.91	Atypical		
	9	202	.20	.99	Typical	5.00	7.06
259	Feb. 9	130	.5	3.85	Typical		
	15	130	.1	.77	No effect		
	23	146	.3	2.05	Typical		
	Mar. 3	....	....	....			
	9	158	.20	1.27	Typical	5.00	5.65
	Optimum		.175	.95		5.72	7.5

Rats Seven to Eight Months Old

Rat	Date	Weight	Dose CC.	CC. Per Kg.	Result	Rats Per CC.	Units Per CC.
174	Feb. 9	232	.20	.86	Typical	5.00	8.30
	15	236	.175	.74	No effect		
	23	236	.175	.74	Atypical		
	Mar. 3	208	.25	1.2	Typical		
	9	206	.20	.97	Typical		
175	Feb. 9	234	.3	1.28	Typical		
	15	232	.150	.65	No effect		
	23	226	.2	.89	Atypical		
	Mar. 3	230	.225	.97	Typical	4.45	7.30
	9	234	.20	.86	Typical ? (Short)		
176	Feb. 9	....	....	....			
	15	....	....	....			
	23	....	....	....			
	Mar. 3	158	.2	1.27	Typical	5.00	5.65
	9	....	....	....			
178	Feb. 9	194	.4	2.06	Typical		
	15	190	.125	.66	No effect		
	23	168	.225	1.34	Typical		
	Mar. 3	228?	.175	.77	Atypical		
Sick	9	156	.2	1.28	Typical	5.00	5.57
180	Feb. 9	220	.5	2.27	Typical		
	15	222	.10	.45	No effect		
	23	218	.25	1.15	Typical		
	Mar. 3	....	....	....			
	9	230	.20	.87	Typical	5.00	8.22
	Optimum		.20	.86		5.00	8.30

Rats Nine to Ten Months Old

Rat	Date	Weight	Dose CC.	CC. Per Kg.	Result	Rats Per CC.	Units Per CC.
141	Feb. 9	234	.2	.86	Typical	5.00	8.35
	15	230	.2	.87	Atypical		
	23	232	.175	.75	Atypical		
	Mar. 3	....	....	....			
	9	242	.25	1.03	Atypical		
145	Feb. 9	220	.3	1.36	Typical		
	15	210	.175	.84	No effect		
	23	226	.2	.89	Atypical		
	Mar. 3	216	.3	1.39	Typical		
	9	226	.25	1.11	Typical	4.00	6.46
146	Feb. 9	236	.4	1.69	Typical		
	15	240	.15	.63	No effect		
	23	244	.225	.92	Atypical		
	Mar. 3	256	.275	1.07	Atypical		
	9	264	.3	1.13	Typical	3.33	6.30
147	Feb. 9	....	....	....			
	15	274	.125	.46	No effect		
	23	276	.25	.91	Atypical		
	Mar. 3	278	.25	.90	Atypical		
	9	278	.3	1.09	Typical	3.33	6.52
148	Feb. 9	276	.5	1.81	Typical		
	15	274	.1	.37	No effect		
	23	280	.3	1.07	Typical		
	Mar. 3	282	.2	.71	Almost no effect		
	9	288	.25	.87	Typical (Short)	4.00	8.23
	Optimum		.2	.86		5.00	8.35

Rats Eleven to Twelve Months Old

Rat	Date	Weight	Dose CC.	CC. Per Kg.	Result	Rats Per CC.	Units Per CC.
106	Feb. 9	220	1.	4.55	Typical		
	15	226	.2	.89	Atypical (almost no effect)		
	23	230	.3	1.30	Atypical		
	Mar. 3	236	.4	1.70	Atypical		
	9	232	.6	2.58	Typical	1.67	2.76
120	Feb. 9	240	.8	3.33	Typical		
	15	232	.3	1.29	Typical (Short)	3.33	5.52
	23	222	.4	1.8	Typical		
	Mar. 3	220	.25	1.13	Atypical		
	9	226	.275	1.22	Atypical (typical?)		
121	Feb. 9	240	.6	2.50	Typical		
	15	228	.4	1.75	Typical		
	23	222	.35	1.58	Typical		
	Mar. 3	220	.3	1.36	Typical	3.33	5.23
	9	222	.25	1.12	Typical ? (Short)		
126	Feb. 9	266	.4	1.50	Typical (Short)		
	15	268	.5	1.85	Typical		
	23	266	.2	.75	Atypical (almost no effect)		
	Mar. 3	268	.35	1.30	Typical (Short)		
	9	268	.3	1.12	Typical	3.33	6.39
	Optimum		.3	1.12		3.33	6.39

Table II. Shows the values in the various age groups for the number of *Rats per CC.* of follicular fluid extract. These are the values which would be used in stating the strength of an extract if the weight of the rat were not taken into account. The deviation from the mean is given for each age group.

TABLE II

Based on Rats Regardless of Weight.
Arranged According to Age Groups.

	AGE* 2-3	AGE 3-4	AGE 7-8	AGE 9-10	AGE 11-12	MEAN
Optimum value *rats per cc.*...	8.00	5.72	5.00	5.00	3.33	5.41
Deviation from the mean ...	48.0%	5.7%	7.6%	7.6%	39.5%	

Table III shows the values obtained in each age group for the number of Allen and Doisy *Rat Units per CC.* of follicular fluid extract. These values are based on the 140 gram rat as the standard. The deviation from the mean is also shown.

TABLE III

Based on the 140 Gram Rat as the Standard.
Arranged According to Age Groups.

	AGE 2-3	AGE 3-4	AGE 7-8	AGE 9-10	AGE 11-12	MEAN
Optimum value *rat units per cc.*	7.15	7.50	8.30	8.35	6.39	7.54
Deviation from the mean.....	5.2%	0.5%	10.1%	10.7%	15.3%	

By examination of Table II it will be noted that when the weight of the rat is not taken into account there is a wide variation in the results of tests for potency of follicular fluid. The age group 2-3 months shows a variation from the mean of 48.0 per cent, and the age group 11-12 months shows a variation of 39.5 per cent. When the weight of the rat is taken into account, as is done in Table III, the variation from the mean is only 5.2 per cent in the 2-3 months age group and 15.3 per cent in the 11-12 months age group. In the other three age groups the variation is not great in either table and the reason for this is

* Age in months.

undoubtedly that the rats in these three groups are of nearly the same weight.

This experiment leads us to conclude that the effective dosage of follicular fluid extract varies directly as the weight of the rat. The experiment also shows that rats may be used regardless of age if they are in the prime of life. This statement must be qualified, however, by stating that only rats in which the oestrous cycles are regular with the four to six-day rhythm, before ovariectomy, should be considered to be in the prime of life. This qualification rules out many rats younger than three months, for usually the oestrous cycles have not become regular until three months of age. The young rats used in this experiment were probably better than average in sexual development. They were selected from a group of 24 rats of the same age because they were the first to show opening of the vaginas. This experiment as well as some of our other work indicates that after 11 to 12 months of age the rat is no longer in the prime of life and should not be used for standardization of follicular fluid. As a general statement it may be said that rats between the ages of three and eleven months are the best for standardization.

In order to express the potency of our extracts of follicular fluid in terms of the Allen and Doisy *rat unit*, which is based on a rather small rat of 140 grams weight, it is necessary to take the weight of the rat into account and to use the factor, weight of the rat divided by 140 grams.

It is a pleasure to express our gratitude to Dr. E. M. Houghton, Director of the Medical Research Laboratories, whose interest in this problem has enabled us to carry out this work.

SUMMARY

1. The results are shown in an experiment on 24 rats in a period of five weeks, to determine whether or not the effectiveness of injections of extract of follicular fluid varies with the age of a rat and with its body weight.

2. The experiment indicates that the dosage of extract of follicular fluid should vary directly as the weight of the rat.

3. The age of the rat is of importance only to the extent that it should have reached sexual maturity and should not have passed the prime of life.

4. For standardization of extract of follicular fluid the best rats are those between three and eleven months of age and whose oestrous cycles are regular with the four to six-day rhythm, before ovariectomy.

5. In order to have a uniform standard we have adopted the Allen and Doisy *rat unit*.

6. Potency of preparations is computed in terms of the Allen and Doisy *rat unit* by using the factor: weight of the rat divided by 140 grams.

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THE EFFECT OF PITUITARY PREPARATIONS ON THE BLOOD SUGAR CURVE AND BASAL METABOLISM

K. M. BOWMAN AND G. P. GRABFIELD

From the Laboratory of Internal Medicine in the Boston Psychopathic Hospital

In a study of the possible effects of pituitary substances on metabolism we have previously considered the nitrogen metabolism (1). The present study is devoted to possible effects on the carbohydrate and basal metabolism.

For measurement of the carbohydrate metabolism we have used the blood sugar curve of Janney and Isaacson (2). Blood sugar determinations were made by the method of Folin and Wu. While this method of study of the carbohydrate metabolism has been criticized by various observers, we can at least get some information from this method if changes are consistently produced.

Basal metabolism determinations were made with the Roth modification of the Benedict portable apparatus for the determination of oxygen consumption. The results are expressed in per cent of normal according to the Dubois scale.

The patients used were partly obese and partly of normal stature. Some of these patients were suffering from probable endocrinopathies. The details of stature as far as they concern this work are given in the accompanying table, were under standard hospital regime. No effort was made to restrict or modify the diet. The patients were not confined to bed.

Products of Armour & Company bought in open market were used. They are designated as follows: Anterior Pituitary, Posterior Pituitary, Whole Pituitary and Pituitrin. The first three are desiccated powders, the last a fluid in ampoules.

It is to be noted that there is a predominance of minus values in these patients, and under these conditions certain changes seem to be fairly constant. It has been previously noted (3) that patients suffering from mental disorders tend to have low basal metabolic rates without evidence of myxedema or hypothyroidism. In the five experiments with anterior pituitary one showed no change in metabolic rate, three showed a

Table Showing Blood Sugar and Basal Metabolism Before and After Pituitary Administration.

Case No.	Age	Sex	Weight	Height	Blood Sugar Curve				Basal Metabolic Rate	Drug and Dosage Per Diem	Blood Sugar Curve				Basal Metabolic Rate
			Lbs.	In.	Fasting	1st Hour	2nd Hour	3rd Hour			Fasting	1st Hour	2nd Hour	3rd Hour	
6	14	M	198	64	99	136	100	114	—6	ANT. PIT. Grs. j for 30 days	96	126	101	112	—1
7	26	F	154	61	...	...	...	...	—1	Grs. v for 10 days; grs. xv for 16 days	...	...	...	...	+10
8	34	F	205	65	130	200	183	167	—5	Grs. x for 3 days; grs. xx for 10 days	139	188	126	135	—5
9	21	F	140	66	130	168	72	94	—18	Grs. ij for 18 days	73	100	80	75	—6
5	10	F	96	48	106	98	119	139	—21	Grs. i for 4 days	...	...	...	...	—31
5	10	F	96	48	...	...	...	...	—21	POST. PIT. Grs. ij for 12 days	...	...	...	...	—27
9	21	F	140	66	130	168	72	94	—18	Grs. ij for 12 days	125	71	87	99	—16
1	19	M	158	69	95	93	95	107	—8	WHOLE PIT. Grs. x for 7 days; grs. xx for 10 days	97	98	101	125	100
2	43	F	142	62	...	...	...	...	—25	Grs. v i. d. for 16 days; grs. x for 14 days	...	...	...	...	—23
3	20	F	229	73	100	134	140	114	—12	Grs. xx for 10 days	103	116	153	131	—8
4	18	F	175	63	115	122	133	132	+15	Grs. xx for 11 days	101	138	117	122	—3
5	10	F	96	48	100	121	105	114	+2	Grs. xx for 19 days	...	...	...	...	—18
15	17	F	133	62	...	...	...	...	—21	Grs. xv for 14 days	93	100	69	91	...
17	50	F	254	61	105	78	73	97	—11	Grs. xv for 31 days	...	...	...	...	—6
					...	...	...	...	+12	Grs. xxv for 7 days	...	...	...	...	+11
9	21	F	140	66	130	168	72	94	—18	PITUITRIN (SURG.) 1 cc. intranasally by tampon for 12 days	107	91	91	79	—15
9	21	F	140	66	111	87	79	98	—17	2 cc. for 5 days	92	95	60	59	?
										2 cc. for 5 days (1 cc. ½ hour before test)	100	69	90	80	—6
6	14	M	198	64	99	136	100	114	—6	2 cc. for 6 days	99	126	133	86	+10
										2 cc. for 6 days (1 cc. ½ hour before test)	100	161	95	129	+12
6	14	M	198	64	74	140	108	91	—6	2 cc. for 4 days	92	99	96	98	—2
										2 cc. for 4 days (1 cc. ½ hour before test)	102	151	112	107	—3

definite rise in rate, and one showed a lowering. Whole pituitary showed in five out of seven experiments a slight rise of rate. Pituitrin showed in every one of four experiments a rise in rate. It is believed by some observers that this change in metabolic rate after the injection of pituitrin, though small in amount, is dependent on the integrity of the thyroid (4).

In so far as they go these experiments confirm the previous ones in regard to a slight rise in basal metabolic rate after the administration of pituitary preparations. We were unable to get any definite information about the sugar metabolism from these experiments.

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Book Reviews

THE CHEMICAL AND PHYSIOLOGICAL PROPERTIES OF THE INTERNAL SECRETIONS. E. C. Dodds and F. Dickens 1925. Oxford University Press, New York and London. P. 214.

The authors have assembled the data on the methods of preparation and physiological properties of the internal secretions in an excellent manner. The results of the more important investigations on insulin, tethelin, pituitrin, thyroxin, adrenaline, and the ovary are included in this text. Secretion, spermine and the parathyroids are briefly discussed. The bibliography contains many valuable references. This book is heartily recommended as an excellent treatise on the subject.

CONTRIBUTION A L'ETUDE DES DYSTROPHIES DE LA PUBERTE. G. Boulanger-Pilet, 1924. Louis Arnette, Paris.

The author offers a well written, succint review of the literature—confined largely, however, to French writers—together with a record of a considerable number of personal clinical observations. He takes up the involvement of the skeletal structures and the adipose tissue in the pubertal dystrophies. Their origin is then discussed from both the endocrine and the nervous points of view. The work concludes with a seven page bibliography. Special importance is ascribed to the gonads among the endocrine factors and to syphilis in the genesis of disorders dependent upon nervous influences.

Abstracts

Action of the small and large doses of adrenaline upon the motility of the small intestine of man. Danielopolu (D.), Simici (D.) & Dimitriu (C.), Compt. rend. Soc. d. Biol., 1925, **92**, 1146-1148; Abst., Rev. franc. d'Endocrinology, **6**, 436.

Small doses of adrenaline affect the parasympathetics exclusively while large doses have an effect predominantly upon the sympathetics. Thus small doses retard cardiac rhythm, decrease blood pressure and exaggerate gastric and oesophageal motility, while the larger doses accelerate the heart rhythm, raise the blood pressure and inhibit the stomach and oesophagus. The work of the authors shows that these conclusions are applicable also to the action of adrenaline upon the small intestine of man. An intravenous injection of 1 cc. of a 1/300,000 of adrenaline exaggerates the amplitude of the peristaltic contractions. A much larger dose produces a marked diminution of the contractions. Occasionally the peristaltic contractions disappear entirely.

Experiments with adrenal insufficiency. Hartman (F. A.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, **23**, 467-468.

Seventeen adrenalectomized cats lived on the average about 50 hours after operation when untreated. Cats treated with injections of cortical extract, obtained with alcohol, ether, glycerol and olive oil, lived to varying periods up to 90 hours. Twenty-two cats treated with saline extracts of cortex lived on the average 146.6 hours.—J. C. D.

Action of adrenalin, pituitary extract, and histamin on capillaries of frog tongue (Untersuchungen über die Wirkung von Adrenalin, Hypophysenextrakt und Histamin auf den Blutstrom in den kleinsten Gefässen der Froschzunge). Killian (H.), Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1925, **108**, 255-279.

Adrenalin applied directly or given subcutaneously produced contraction of arteries, arterioles and arteriole capillaries. Pituitary extract applied locally or given by subcutaneous or intravenous injection caused general vaso-constriction. Histamin brought about general vaso-dilatation extending to the venous capillaries. Effects were recorded photographically.—G. E. B.

Histological changes in the adrenal glands of guinea pigs subjected to scurvy and severe inanition. Medes (Grace) & Lindsay (Blanche), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, **23**, 393-394.

These glands show hemorrhagic infiltration between the columns of cortical cells at the periphery of the medulla. There is also cell degeneration but this is not so striking. These changes agree with those described by McCarrison in 1921 in similar experiments.

The action of adrenine on the nitrogen, creatinine, and creatine excretion (Zur Frage der Wirkung des Adrenalins auf die Stickstoff-, Kreatinin- und Kreatinausscheidung). Palladin (A.) & Tichwinskaja (W.), Arch. f. d. ges. Physiol. (Berl.), 1925, **210**, 436-441.

If adrenine is injected once daily in gradually increasing doses into rabbits, it has no influence on nitrogen or creatinine excretion with normal diet. If it is injected twice daily, with rapidly increasing doses, there is on the other hand markedly increased excretion of nitrogen and creatinine, and further, creatinuria.—A. T. C.

Tolerance for epinephrine. Ricaldoni (A.), Bull. Soc. Méd. d. hôp. (Par.), 1925, **49**, 1627-1628; Abst., J. Am. M. Ass., **86**, 724.

Ricaldoni examined a patient with asthma who had been in the habit of injecting himself with epinephrine for 13 years (0.006 gm. daily for 10 years, then from 0.009 to 0.012 gm. daily for 3 years). This epinephrine addiction did not seem to have induced marked changes in the cardiovascular apparatus. The man was thin and pale, but his earning capacity was unimpaired and there was no hypertension.

Addison's disease, with report of cases. Swan (W. H.) & Bortree (L. W.), Boston M. & S. J., 1926, **194**, 712-714.

A brief consideration of seven patients, all of whom had tuberculous histories. All patients died. Substitution therapy of various kinds was tried in six cases. In one case pituitary extract relieved the patient somewhat, but in the other cases no result could be observed.—J. C. D.

The blood sugar level and the epinephrin content of the suprarenals of the rabbit in diphtheritic intoxication. Mikami (S.), Tohoku J. Exper. Med. (Sendai), 1925, **6**, 299-324.

Diphtheria toxin (0.1 cc.) was injected intravenously into rabbits (0.5-5.5 cc. per kgm.). The lethal dose for the guinea pig is 0.12 cc. In doses above 3 cc. the blood sugar increased 81% or more, reaching its maximum in 2 to 5 hours. In smaller doses 0.8-3 cc. diluted with saline (0.024-0.2 kgm.) hyperglycemia, averaging 133%, occurred in 2 to 6 hours. Rabbits died in 24 hours. The upper limit of original toxin fluid not capable of calling forth hyperglycemia was 0.05 cc. per kgm. In one series where 0.02-0.05 cc. per kgm. was used, rabbits were killed 24-29

hours later. Blood sugar was low, liver glycogen and epinephrin of adrenals low as well. As a control, rabbits were injected with the same quantity of bouillon fluid with negative results. As a second control the toxin was neutralized by antitoxin and the same quantity injected with negative results. Double splanchnectomy prevented any marked rise of the diphtheria hyperglycemia. The author explains diphtheria hyperglycemia as being of central origin. He further studied the epinephrin content of the adrenals hourly in the course of diphtheria poisoning, which brought on depletion of the epinephrin storage of the adrenals. The loss was small the first hour, reached its peak about the sixth hour, decreased again so that it reached its normal at about the eighth or ninth hour of the poisoning. As the blood sugar went up, the epinephrin content of the adrenals went down, the hyperglycemia curve slightly preceding; finally both curves came together in the ninth and tenth hour. Toward the end of life, blood sugar content and epinephrin store were greatly decreased, liver glycogen remaining the same. In one group of rabbits the splanchnic nerves on one side were previously divided; one-half of these were killed at the sixth hour, the other half at the twenty-first and thirty-sixth hour of intoxication. In the first group the epinephrin of the intact side was greatly decreased and on the denervated side almost unchanged. In the second series the absolute quantity and percentage content of epinephrin was the same in both glands. In such a long period of poisoning, denervation could not protect the gland from loss of epinephrin. In the dying period of poisoning about 2/5 of the epinephrin storage was gone. When an animal is gradually poisoned with diphtheria toxin and lives a day or more in a somewhat moribund state, not hyperglycemia but hypoglycemia occurs. This persists 24 hours or more. The epinephrin of the adrenals as well as liver glycogen are markedly diminished. Double splanchnectomy does not protect the animal from the diminution of these 3 substances.—H. J. John.

The ovarian follicular hormone: a study of variation in pig, cow and human ovaries. Allen (E.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, **23**, 383-387.

The author used as a standard for comparing the potency of different samples of follicular hormone the least amount of lipoid extract that will produce a definite physiological reaction in the spayed adult rat. Using this standard he finds in sows a variation from 28 rat units before ovulation to 2.1 units after ovulation, and in cows from 4.6 units before to a non-measurable amount after. In the human the highest value, 7 rat units, was during the third week from the start of the previous menstruation. In the fourth week the yield was 2 units. In women, then, the hormone content is high and it does not vary as abruptly as in cows and sows.

"This might account in part for (1) the longer duration of the menstrual cycle (in man), (2) the longer portion of the cycle during which mating instincts may be in evidence, and (3) the continuance of the anabolic and secretory phase for a considerable period after ovulation."—J. C. D.

The menstrual cycle in the monkey; effect of double ovariectomy and injury to large follicles. Allen (E.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, **23**, 434-436.

The work was carried on with five monkeys. The author summarizes and concludes: (1) The removal of both ovaries on the first day of menstruation had no apparent effect on that period. (2) Double ovariectomy or injury to large follicles dated toward the end of, or immediately after, the follicular phase of the cycle was followed by apparently typical menstrual bleeding. These experimental menses appeared from 5 to 13 days before the expectation as calculated by the length of previously observed cycles and by Corner's mode for cycle length to 27 days. (3) External coloring and swelling disappeared after double ovariectomy. From these data it is concluded that menstruation is probably due to an absence of follicular hormonal stimulus after it has been acting for a certain period of time. In this connection it should be noted that the presence of the follicular hormone has been demonstrated in human corpora lutea. It is quite possible that the corpus of the monkey may also continue to secrete the follicular hormone, thus postponing the onset of menstruation.—J. C. B.

Ovarian grafting. Bell (W. B.), Surg., Gynec. & Obst. (Chicago), 1925, **41**, 706-710.

Ovarian grafting rather than complete ovariectomy is recommended in certain cases of salpingo-oöphoritis and non-malignant ovarian neoplasms. In the series of cases reported upon, autoplastic grafts alone were successful. The most desirable location was the body of the rectus muscle. Out of a total of 187 cases, 118 were analyzed. Functional results, or the non-appearance of symptoms of the menopause, were obtained in 80% or 98 of these cases. Menstruation has continued in some cases for as long as seven years after the operation. In two cases the formation of follicular cysts in the grafts was accompanied by menorrhagia.

—M. O. Lee.

Necrosis of the corpus luteum of pregnancy. Brennan (D.) & Cohen (M.), Surg., Gynec. & Obst. (Chicago), 1926, **42**, 228-235.

This may occur in pernicious vomiting of pregnancy, and probably has the same significance as has necrosis of the liver and kidneys in this disease.—A. T. C.

The sexual cycle in the female of mammals. The follicular phase. (Le cycle sexuel chez la femelle des mammifères. Étude de la phase folliculaire). Courrier (R.), Arch. de biol. (Liége & Par.), 1924-25, **34**, 369-473; Abst., Physiol. Abst., 1926, **10**, 605.

In the adult female of mammals the generative organs and mammary gland undergo cyclic changes which are chronologically and intimately connected with the maturation of the Graafian follicles and the formation of the corpus luteum. During the former process (follicular stage) the mammary and uterine glands become hypertrophic, the oviduct enters a phase of intense secretion, and the vaginal epithelium actively proliferates. These phenomena are considerably accentuated during the luteinic stage. They are very likely brought about by a substance (folliculine) which can be extracted from the liquor folliculi and used for control experiments.

The specific dynamic action of protein in children before and during the period of puberty. Göttche (O.), Klin. Wchnschr. (Berl.), 1925, **4**, 2062-2064; Abst., Chem. Abst., **20**, 228.

The sexual hormone and the thyroid hormone increase the basal metabolic rate and decrease the specific dynamic action of protein. The action of the hypophyseal hormone is the reverse of the above. In short, the hypophysis is antagonistic to the thyroid and to the sex glands. Ingestion of protein by adults increases the oxidation process by 30%. In young children (prepuberty period) protein calls forth only a 20% increase in the oxidation rate. In such children the hypophysis and thyroid are active; but the sexual hormone is absent. The action of the hypophysis is predominant. The early stages of puberty are characterized by a 10-35% increase in the basal metabolic rate and a marked decrease in the specific dynamic action of protein, the mean value being about 5% as compared to 30% in adults. The influx of the new hormone has destroyed the previously existing balance between the hypophysis and thyroid with a temporary suppression of the hypophyseal activity. The period of puberty is associated with a tendency to establish a new balance between the endocrine organs so that the basal metabolic rate steadily decreases to normal and the specific dynamic action of protein steadily rises to the adult value of 30%.

The corpus luteum as the source of the follicular hormone. Johnston (C. G.) & Gould (V. L.), Surg., Gynec. & Obst. (Chicago), 1926, **42**, 236-240.

The amount of care exercised in collecting corpus luteum material is an important factor in testing for the follicular secretion. Using rats and rabbits, no noticeable changes were produced in the genital tract by injection of the alcohol-ether-acetone extract of carefully collected corpora lutea of pigs. Neither pregnancy, nor

the size, consistency, nor color of the corpora lutea had any effect on the results obtained, while repeated positive results have been obtained with the corresponding extract of the liquor folliculi of hog ovaries. It is concluded that the corpus luteum does not produce the active internal secretion which produces hyperplasia of the uterus and vagina.—A. T. C.

Estrus-inducing hormone. Lacquer (E.), Hart (C. P.), de Jongh (S. E.) & Wijsenbeek, Deutsche med. Wchnschr. (Berl.), 1926, **52**, 52-54; Abst., J. Am. M. Ass., **86**, 727.

The authors confirm Zondek and Brahn's discovery of a water soluble hormone of the estrual cycle. They suggest the name "menformon" for it, but want it reserved exclusively for such preparations as contain in 1 mgm. of substance at least ten doses sufficient to provoke the estrual cycle in a castrated mouse. The pure preparations contained too little substance to be analyzed chemically. They believe that the hormone probably contains no protein nitrogen, phosphorus or cholesterol.

The use of corpus luteum to prevent nausea in radiation therapy of uterine conditions. Lafferty (R. H.) & Phillips (C. C.), Am. J. Roentgenol. & Therapy (N. Y.), 1925, **14**, 381-486.

The patients in the 16 cases reported ranged in age from 25 to 45 years. Of these, 10 were entirely relieved, 4 were improved and 2 were unimproved. One of the unimproved patients was 25 years of age, the other 45. All of these 16 patients were known to become very much nauseated following small doses of roentgen rays, when corpus luteum was not used. Some of those listed as completely relieved were given the extract on alternate treatments and each time it was not given they were very much nauseated. In making this report the authors assert that they realize that the number of cases is too small to warrant positive conclusions, but the results were so uniformly good that it seemed wise to report them in order that others may try the same treatment. It is important, in their opinion, that the injections be given intravenously, 1 to 2 cc. being used immediately after radiation treatment.

—Author's Abstract.

Ovarian Grafts. Pettinari (V.), Arch. ital. de Biol. (Pavia), 1924, **74**, 62-72.

Pettinari has made a large number of grafts of ovaries in several species of animals. He reports the expected signs of secretion of grafts and correlates these results with a histologic study. Follicular maturation with corpus luteum formation may occur in autoplastic grafts: follicular atresia is characteristic of heterosexual grafts. He concludes that the follicles are the principal source of hormone production, the corpus luteum having no par-

ticular endocrine action. He believes that the hormone from the follicles is the only one necessary for hypertrophy and secretion of the mammary glands.—E. Allen.

Fate of ovarian graft. Rheaume (P. Z.), Union méd du Canada (Montréal), 1925, **54**, 686-690; Abst., J. Am. M. Ass., **86**, 518.

Rheaume had opportunity to examine an ovary that had been transplanted into the abdomen after bilateral ovariectomy five years before. After the operation the woman suffered exceptionally severely from the phenomena of the induced menopause. At the recent laparotomy (required for a different disease) the ovary appeared reduced to one-half its former size. It was enclosed in a fibrous capsule but was abundantly supplied with vessels and was well nourished and anatomically almost intact. The physiologic function of the gland, however, had evidently never been resumed. Rheaume thinks that ovarian grafting is worth even less than grafting monkey testicles in men.

Experimental hyperthyroidism and the germ glands in amphibians, with special reference to the primitive interstitial tissue. Speidel (C. C.), Anat. Record (Phila.), 1925, **31**, 65-78.

Frog tadpoles, in which metamorphosis has been hastened by desiccated sheep thyroid, exhibit an increase in the mitotic activity of the intertubular mesenchymal cells. These cells are held to be the progenitors of the interstitial cells. Thyroid treated tadpoles also show a definite, though not conspicuous, increase in the rate of proliferation of spermatogonia and, to a lesser degree, oögonia. The author believes that the effect of hyperthyroidism upon the primitive interstitial cells suggests a part of the mechanism by which early maturity in secondary sexual characteristics is attained by hyperthyroid individuals.—W. J. A.

Release of the sexual cycle, development of the sex characteristics, reactivating action on the senile female organism through ovarian and placental extract (Auslösung des sexualzyklus, Entwicklung der Geschlechtsmerkmale, reaktivierende Wirkung auf den senilen weiblichen Organismus durch Ovar- und Placentaextrakt). Steinach (E.), Heinlein (H.) & Wiesner (B. P.), Arch. f. d. ges. Physiol. (Berl.), 1925, **210**, 598-611.

The experiments reported were made with rats and guinea pigs, the results of which are indicated in the title.—A. T. C.

Rejuvenation. Walker, K. M., Practitioner (Lond.), 1925, **115**, 84-90.

This is a general discussion without experiments or detailed case reports. The author has seen some improvements as a result of ligating the vas deferens, but better results from transplants of

human testicle into the tunica vaginalis. The improvement in these patients is general but not particularly noticeable in the realm of sexual functions. He finds ligation of the vas specially beneficial in paralysis agitans.—J. C. D.

Aqueous solution of ovarian hormone. Zondek (B.) & Brahn (B.), Klin. Wchnschr. (Berl.), 1925, **4**, 2445-2446.

A method described in abstract for the preparation of a water soluable extract of placenta or ovarian follicular fluid. The lipoid residues from alcohol, ether and chloroform extractions were boiled in acetic acid. The filtrate was cooled, causing a percipitate to settle out. This was then cleared and neutralized. It was then concentrated in vacuo and used for injections. No statement is made of the number of tests nor the yield of active material. The extract was tested for activity by injections into spayed mice, the oestrous reaction of the vaginal epithelium being the criterion of a positive extract. Intravenous injections into mice and guinea pigs were not injurious.—E. Allen.

The hypophyseal cachexia—A synthetic review (La chasessia ipofisaria—Rivista sintetica). Bolsi (D.), (Siena), 1924, S. Bernardino.

The syndrome discovered by Simmonds (1914) is more characteristic in women than in men, owing to the partial and finally the total disappearance of menstruation before the climaterium. Other symptoms in progressive cachexia are: loss of weight, modification of the skin (which becomes light yellow), early senility, loss of body hair—very seldom the head hair, loss of teeth (partial or total), sometimes atrophy of the lower jaw, a severe degree of anemia, sometimes eosinophilia and at times hypethermia. In the nervous system one finds asthenia and adynamia and even apathy and psychomotor torpor. The syndrome is hardly ever complete. In a case of quick growing tumor the hair symptoms as well as the cachexia may not show. At times there is no note of senility. Fever occurs only in cases of septicemia. Polydipsia and polyuria and even acromegalic symptoms may appear, preceding the cachexia. A case reported by Mieremer showed only a condition of lethargy and lesion of the hypophysis. In a rapidly growing tumor the process may be very quick, but usually is very slow. Arrest of symptoms is seldom found. Hypophyseal opotherapy seems to be of some value though never entirely curative. The syndrome is oftener found in women and it might be referred to embolism (often after confinement) with consequent fibrosis of the gland (Simmonds). Fahr contends instead for an inflammatory process. Lesions of other glands have often been found, especially the thyroid, the adrenals and the ovaries.—G. Vercellini.

A case of sclerosis of the anterior lobe of the hypophysis with cachexia (Un caso di sclerosi del lobo anteriore dell' ipofisi-considerazioni sulla cachassia ipofisaria.) Bolsi (D.), (Siena), 1925, S. Bernardino.

A case of cachexia in a woman who had dementia praecox from the age of 20 years and a torpid tuberculous lesion at the apex of her right lung diagnosed at her 55th year. At autopsy the anterior lobe of the hypophysis appeared very much reduced, leaving an empty space in the sella. The posterior lobe appeared normal, but there was sclerosis of the pars intermedia and even more of the anterior lobe. The total weight of the gland was 32 cgm. Discarding the mental condition as well as the torpid tuberculous lesion as a cause of cachexia, the condition would appear to have been due to the hypophyseal lesion.—G. Vercellini.

Late eunucoidism and syphilitic dyspituitarism (Eunucoidismo tardivo e dispituitarismo sifilitico). Coppola (A.), (Siena), 1925, S. Bernardino.

The patient reported by the author was of a family in which polysarcia and familial deafness were found in the last four generations. The patient contracted syphilis when 28 years of age. He was under treatment only three months. He was married at the age of 30 and had five children, three of whom were living. From the ages of 28 to 30 he gained 20 kgm. in weight. At 48, following a severe fronto-occipital headache (four months) he lost 34 kgm. in weight, 25 teeth were lost in a few weeks and he had severe polyuria and polydipsia (two months). He improved on mercurial treatment, but two years after had a gummatous osteitis of the nasal bones, which improved under new mercurial treatment. At 50 he lost his potentia and three years later his voice had lost its male timbre, and all the hair of the body (head excepted) had fallen. Finally he presented asthenia and hypersomnia. The x-ray showed diffused basilar hyperostosis. The pluriglandular syndrome can be explained by the action of the hypophysis on the gonads and of these on the thyroid as well as on the adrenals.

—G. Vercellini.

Relation of the pituitary to carbohydrate metabolism (Zur Frage einer Beziehung der Hypophyse zum Kohlenhydratstoffwechsel). Fukui (T.), Arch. f. d. ges. Physiol. (Berl.), 1925, **210**, 427-431.

Injection of posterior and of anterior pituitary extracts had no definite influence on the liver glycogen of normally fed rats, and did not influence the effect of thyroid on liver glycogen.—A. T. C.

Mid-brain changes in diabetes insipidus (Ueber Zwischenhirnveränderungen bei Diabetes insipidus). Kiyono (H.), Arch. f. path. Anat. u. Physiol. (Berl.), 1925, **257**, 477-489.

Report of the case of a 59-year-old woman who had shown symptoms of diabetes insipidus for 13 years. Her father died of diabetes, her mother of carcinoma of the uterus. Another member of her family had Addison's disease. The outstanding symptoms in this case were thirst, polyuria, intestinal disturbances, gradually increasing weakness, staggering gait, partial deafness. The anatomical basis for the diabetes insipidus was found in a marked round cell infiltration of the tuber cinereum. The cell nuclei in the tuber cinereum, nucleus tuberis, nucleus supraopticus and the nucleus paraventricularis were markedly changed. There was pronounced atrophy of the posterior lobe of the hypophysis, which the author believed to be a result of the long continued intense injury to the tuber cinereum. The thyroid showed atrophy of the acinar epithelium and marked fibrosis. Other glands of internal secretion also showed pathological changes. Chronic interstitial nephritis was present. The author believes that his findings justify the conclusion that nerve fibers pass from the tuber cinereum peripherally to the hypophysis.—J. P. S.

A simple method for the biological assay of hypophysis preparation. Loewe (S.) & Ilison (M.), Klin. Wchnschr. (Berl.), 1925, **4**, 1692; Abst., Chem. Abst., **20**, 448.

Small pieces of frog skin, immersed in a nutrient medium, react toward hypophysis extract exactly as does the intact frog; the skin becomes deeply pigmented. Examination of such skin sections under the microscope shows that this coloration is caused by an excitation of the dormant pigment cells with a consequent pigmentation. A maximum conversion of dormant into active pigment cells occurs in 15 minutes. The percent conversion of dormant into active, fully pigmented cells, in 15 minutes is directly proportional to the strength of the preparation. A good preparation gives 100% conversion. This method of assay is preferable to the uterus contraction method because the reaction is specific for hypophyseal extract.

The presence of an oxytocic substance (posterior hypophysis extract) in cerebrospinal fluid. Shapiro (S.), Arch. Neur. & Psychiatry (Chicago), 1926, **15**, 331-340.

Of 28 cerebrospinal fluids obtained from 25 different patients, none caused an oxytocic effect on the virgin guinea-pig uterus. They had, indeed, a tendency to inhibit contraction. The intravenous injection of pituitary extract failed to cause an increased secretion of the active principle present in the posterior lobe of the hypophysis into the cerebrospinal fluid within three minutes after injection.—R. G. H.

Hypophysial fat dystrophy with hyperglycemia and glycosuria. Shapiro (S.) & Kliatshco (M. G.), Arch. Neurol. & Psychiat. (Chicago), 1926, **15**, 85.

The patient was a woman 47 years of age with typical hypophysial fat dystrophy associated with a tumor in the region of the hypophysis. This was definitely proved by roentgen and careful neurological examinations. In addition hyperglycemia and glycosuria were present. It is the general belief that the fat dystrophy which occurs on Fröhlich's syndrome results from increased fat formation consequent to the high glucose tolerance that usually is seen in these cases. The development of increased fat deposits in the presence of an apparent diabetes mellitus, therefore, is offered as evidence that the fat dystrophy is not dependent upon an increased glucose tolerance for its formation.—Authors' Abstract.

The chemical regulation of the heart beat by the liver (Ueber die chemische Regulierung des Herzschlags durch die Leber). Asher (L.), Arch. f. d. ges. Physiol. (Berl.), 1925, **209**, 605-606.

When all sources of error are excluded, the perfusate from the liver still contains a specific substance which, tested on the frog's heart, augments and accelerates the beat.—A. T. C.

Studies on the influence of diet on the action of certain internal secretions. III. Insulin and adrenine action with acid as compared with basic diets (Studien über den Einfluss der Ernährung auf die Wirkung bestimmter Inkretstoffe. III. Insulin- und Adrenalinwirkung bei Verabreichung "saurer" bezw. "basischer" Nahrung). Abderhalden (E.) & Wertheimer (E.), Arch. f. d. ges. Physiol. (Berl.), 1924, **205**, 559-570.

Rabbits on acid diet (oats) react to insulin much more weakly, as measured by lowering of blood sugar, than others on basic (green food) diet, but adrenine produces a much stronger hyperglucemia in the former. The alkali-reserve is lowered in acid-diet rabbits, and the velocity of settling of the red corpuscles is much slower.—A. T. C.

Influence of diet on the action of certain internal secretions. IV. (Studien über den Einfluss der Ernährung auf die Wirkung bestimmter Inkretstoffe. (IV). Abderhalden (E.) & Wertheimer (E.), Arch. f. d. ges. Physiol. (Berl.), 1924, **206**, 451-459.

Hyperglycemia produced artificially by subcutaneous injection of glucose is maximal with an acid diet and but slight with a basic diet. Fructose and galactose give the same blood sugar curves, no matter what the diet.—A. T. C.

Diabetes and insulin. Banting (F. G.), Can. M. Ass. J. (Montreal), 1926, **16**, 221-232.

The Nobel lecture (Sept., 1925) giving the history of the discovery, the present method of preparation, and that of standardization, the present method of use of insulin in diabetes, evidence from case reports of improvement in carbohydrate tolerance under insulin treatment, and, in one case, that of a young boy, of regenerative acinar and islet changes in the pancreas after a year's insulin treatment, revealed at post-mortem examination following accidental death.—A. T. C.

On the possible iodemetric estimation of insulin. Brand (E.) & Sandberg (Marta), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, **23**, 313-316.

The authors allow an excess of iodine solution to react with insulin previously twice precipitated at the isoelectric point in the presence of a neutral buffer under standard conditions. The amount of iodine used in the precipitation of the insulin which results is estimated by titration. The results obtained by this method so far parallel very closely the values as found by the physiological method.—J. C. D.

The relation of the thyroid gland to the action of insulin. Burn (J. H.) & Marks (H. P.), J. Physiol. (Lond.), 1925, **60**, 131-141.

The experiments were made to test further Macleod's hypothesis that during hypoglycemia produced by insulin the liver discharges glycogen and raises the blood sugar to the normal level. They find that section of both splanchnic nerves in the cat increases the hypoglycemic reaction of insulin. In rabbits when the hyperglycemic reaction to adrenalin is large, the hypoglycemic reaction to insulin is small and vice versa. Thyroidectomy diminishes the adrenalin and increases the insulin reaction. Thyroid feeding, so long as the liver glycogen is not diminished, increases the reaction to adrenalin and decreases the reaction to insulin. In prolonged thyroid feeding if the liver glycogen disappears the hyperglycemic reaction to adrenalin diminishes and the hypoglycemic reaction to insulin increases. The evidence confirms the view that the liver by liberating sugar from its glycogen store antagonizes the hypoglycemia produced by excess of insulin in the circulation.—T. C. B.

Insulin-glucose treatment of surgical shock and non-diabetic acidosis. Fisher (D.) & Mensing (E.), Surg., Gynec. & Obst. (Chicago), 1925, **40**, 548-555.

Three cases of pre-operative, non-diabetic acidosis are reported in which subcutaneous administration of insulin, with glucose given intravenously caused a disappearance of ketosis far more rapidly than glucose alone. In five cases of surgical shock the same treat-

ment caused a rapid and definite disappearance of the typical clinical symptoms.—A. T. C.

II. Physical and chemical studies of human blood from cases of diabetes mellitus. Foshay (L.), Arch. Int. Med. (Chicago), 1926, 37, 18-31.

A study of the physical and chemical changes which occur in the blood of diabetic patients as a result of the anhydremic or hydremic effects of hypoglycemia. Sixty-one samples of defibrinated blood from 22 cases of diabetes mellitus were analyzed for electrical conductivity of whole blood and of blood serum, erythrocyte counts, volumes per cent of serum and cells, average erythrocyte volume, glucose and chlorin concentrations in both serum and erythrocytes, and in some cases the serum carbon dioxid combining power. In young, untreated diabetic patients without arteriosclerosis, anhydremia and diminished alkaline reserve were noted constantly, as evidenced by depression of the electrical conductivities, high erythrocyte counts, diminution in the volume per cent of serum, increase in the volume per cent of cells, diminution of whole blood chlorides, frequently an increase in the corpuscular chlorid, and a diminution of the serum carbon dioxid combining power.

In arteriosclerotic diabetic patients, hydremia was the rule. The electrical conductivities were not depressed, erythrocyte counts were normal or lower, the volume per cent of serum was higher than normal, the average erythrocyte volume was not increased, blood chlorid was not diminished, and the serum carbon dioxid combining power was within normal limits. The blood findings from all patients in diabetic coma were alike regardless of the presence or absence of arteriosclerosis, and represented merely an exaggeration of all the departures from the normal that are customarily present to a much less extent in all young diabetic patients. In young patients with diabetes there is evidence of both anhydremia and diminution of the alkaline reserve at all times, which disappear rapidly under insulin and dietetic therapy. In arteriosclerotic diabetic patients, exsiccation and anhydremia do not occur, and there is no evidence of diminished blood alkalinity until the patient is in coma or nearly so. Anhydremia itself produces acidosis and in the younger patients this is added to the volatile acidosis which results from deranged fat metabolism. Hence the young diabetic patient is always potentially a case of impending diabetic coma. Adequate therapy demands special attention to the fluid intake. The absence of anhydremia in arteriosclerotic patients is believed to be due to arteriosclerotic changes in the kidneys which do not permit the latter to respond to hyperglycemia by excessive diuresis.—Author's Abst.

The chemical nature of insulin. Funk (C.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, **23**, 281.

A precipitate was obtained by treating insulin containing 10 clinical units per mgm. with naphthol yellow S. This precipitate was physiologically active. Study of it indicates that insulin is probably a polypeptide with a molecular weight around 700. It contains one atom of sulphur and 20 of nitrogen.—J. C. D.

Surgical complications of diabetes under insulin treatment. Gager (L. T.), Surg. Gynec. & Obst. (Chicago), 1925, **40**, 630-634.

Use of properly balanced diet and adequate doses of insulin will maintain carbohydrate metabolism sufficient to prevent acidosis, and keep the blood sugar low, thus providing an essential basis of satisfactory wound healing. Infections should be given the benefit of early operation, both from the standpoint of the diabetes and of the surgical condition.—A. T. C.

Action of the pancreas on the vagus [Action due pancréas sur le tonus et l'excitabilité pneumogastrique (Note préliminaire.)] Garrelson (L.), Santenoise (D.) & LeGrand (A.), Compt. rend. Soc. de biol. (Par.), 1925, **93**, 1233-1235.

A preliminary report regarding the effect of the pancreas on the vagus. The removal of the pancreas causes acceleration of the heart rate and decrease of the amplitude. The respiratory rhythm is also affected. An active substance is secreted into the blood stream by the pancreas.—E. Larson.

Hypoadrenalism and dysinsulinism. A new pluriglandular syndrome (Typo-epinephrie et dysinsulinisme. Nouveau syndrome pluriglandulaire). Gougerot (H.) & Peyre (E.), Compt. rend. Soc. de biol. (Par.), 1925, **93**, 1202-1203.

A report of four cases in which there was a low blood sugar (60-67 mgs. per 100 cc.) associated with an abnormal fatigability and vascular hypotension. The mechanism of the condition is obscure. Three of the subjects were syphlitic. The condition was improved by antisyphlitic combined with pluriglandular treatment. It is stated to be important to recognize the relation between the adrenals and the internal secretion of the pancreas.—E. Larson.

The method of action of insulin. I. Insulin and the glucose partition between fluid and non-fluid systems (Zur Frage der Wirkungsweise des Insulines. I. Insulin und die Glucoseverteilung zwischen flüssigen und nichtflüssigen Systemen). Häusler (H.) & Loewi (O.), Arch. f. d. ges. Physiol. (Berl.), 1925, **210**, 238-279.

Glucose added to a suspension of blood-vessel pulp in normal saline, oxalate plasma or serum, remains completely in the liquid

phase. In presence of insulin, 6% of glucose on the average, is bound to the tissue. Glucose added to sodium fluoride ox blood is not bound to the corpuscles; insulin binds it. Human sodium fluoride blood partitions glucose between cells and plasma. Insulin increases the amount bound to the cells. Human red blood corpuscles saturated with glucose give up to glucose-free saline less glucose in the presence of insulin. The degree of insulin action depends on the glucose concentration of the system, the amount of insulin, the proportion of red cells and the nature of the fluid system, the effect in saline being much less than in serum or plasma, while increased concentrations of sodium fluoride inhibit the action. Such changes must be considered before direct action of glucose on carbohydrate can be held demonstrated.—A. T. C.

The method of action of insulin. II. Insulin and the phosphate and potassium content of blood (Zur Frage der Wirkungsweise des Insulins. II. Insulin und der Phosphat- und Kaliumgehalt des Blutes). Häusler (H.) & Heesch (O.), Arch. f. d ges. Physiol. (Berl.), 1925, **210**, 545-549.

Blood dilution through bleeding is produced through a tissue fluid, containing less phosphate and much less potassium than blood. At the height of the action of a subcutaneous injection of insulin the phosphate and potassium content of blood is definitely lowered; this is independent of blood dilution, since it takes place in the absence of dilution. Under similar in vitro conditions in which insulin causes transference of glucose from fluid phase to red cells there is no action on the partition of inorganic phosphate and potassium.—A. T. C.

Embolic gangrene of the extremities in pneumonia. A report of a case occurring in diabetic coma with an observation on the sugar content of cerebrospinal fluid during insulin shock. Kiefer (E. D.), Brigham (G.) & Wheeler (R. R.), Boston M. & S. J., 1926, **194**, 192-199.

The patient received 520 units of insulin in 22 hours during which his blood sugar fell from 1080 mgm. to 56 mgm. per 100 cc. Insulin shock followed and was relieved by glucose. A lumbar puncture made at the time blood sugar was minimum showed 333 mgm. of sugar per 100 cc. compared to the normal of 60 to 100 mgm. This shows that insulin shock is not due to a lack of sugar in the spinal fluid and suggests that the fall in the sugar content under insulin is slower in the spinal fluid than in the blood. The danger of very rapid appearance of coma in diabetics with infections is emphasized together with the need of heavy doses of insulin to meet such a crisis.—J. C. D.

Diabetic and non-diabetic glycosuria in the surgical patient. Menninger (W. C.), Surg., Gynec. & Obst. (Chicago), 1925, **41**, 454-460.

In a series of 47 cases treated before insulin there were 20 deaths. In a series of 22 cases treated with insulin there was one death. Traumatic glycosuria may be effectively treated, when necessary, with insulin.—A. T. C.

Distribution of insulin in the normal and pancreatic diabetic dog. Nothmann (M.), Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1925, **108**, 1-63; Abst., Chem. Abst., **20**, 441.

The pancreas, liver, muscle, blood, spleen, kidney, heart, lung, thyroid, salivary gland, brain and testis of normal dogs were tested for the presence of substances which, acting like insulin, would reduce the blood sugar in rabbits. With one exception (the spleen of one dog) all organs yielded active extracts, whose effects were identical with those of insulin. In the rabbit deprived of food they caused a fall in blood sugar and the glycogen content of the liver and the musculature of normal rabbits was diminished. In animals with pancreatic diabetes the extracts reduced the blood pressure and simultaneously diminished the sugar output through the urine. Extracts prepared from the tissues of dogs with pancreatic diabetes were without insulin-like action with the exception of those prepared from liver tissue. In these animals the amount of active principle in the liver was but slightly less (4.03 units per 100 g. of fresh liver) than that of the liver of the normal animal (4.44 units). To a high degree the amount present in the liver is independent of the glycogen content of the liver and of the time after extirpation of the pancreas. Ether narcosis does not modify the content in insulin-like material. The principle derived from the liver of pancreatic diabetic dogs markedly reduces the glycogen content of liver and muscle of normal rabbits and may lead to convulsions. Injected intra-arterially it changes the blood sugar relationships in both the arterial and venous blood. Injections of the liver extract allowed dogs to live for 24 days after complete removal of the pancreas. Here, blood sugar was reduced, as was sugar excretion, but the glycogen content of the animal remained normal. Apparently the insulin-like substance of the dog with pancreatic diabetes is identical in all respects with that of normal dogs and with insulin.

Studies on the denervated rabbit's iris (Über die Möglichkeit röntgenexperimenteller Verschiebung des physiologischen Inkretgleichgewichts zwischen Pankreas und Nebennieren und ihren Einfluss auf das vegetative System). Risse (O.), & Poos (F.), Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1925, **108**, 121-148.

Following irradiation of the rabbit active substances are thrown

into the blood stream which can affect strikingly the denervated and completely atropinized pupil in producing both mydriasis and miosis. The mydriatic substance is probably adrenalin. The miosis, peripherally produced, is due to a hormone which in addition can break through an atropin paralysis and quickly restore sensitiveness to light. It is suggested that this hormone is produced by the pancreas.—G. E. B.

A clinical and pathologic study of twenty-six cases of diabetes. Root (H. F.), & Shields (W.), Boston M. & S. J., 1926, **194**, 45-53.

Analysis of the etiology shows obesity as a factor in all except one case. Syphilis, heredity and acute infections played an inconsistent part. One case was associated with hyperthyroidism, which had preceded the diabetes. The average duration of the disease was 9.2 years. The highest mortality was in the young and the old. The greatest danger period was during the first two years of the disease. In ten cases death probably would have been preventable with a better knowledge of the disease and its dangers. In the pathology the striking thing is the evidences of regeneration in the Islands. We have here a cycle of destruction and regeneration of active cells similar to that found among the parenchymal cells of the liver. This is strikingly shown in "bronze diabetes," where the toxic agent, hemofucsin, is attacking both liver and Island cells and where the results can be seen to be alike. The authors offer a new interpretation of the pathology of the pancreas in diabetes mellitus. The long continued action of an injurious agent (or possibly excessive functional activity) causes a gradual destruction of islands, and at times of acinar, cells. New cells are formed to take the place of those destroyed, only to be exposed to the injurious influence with consequent pathologic change. Their injury is followed by the production of more new cells. The rarity of death from uncomplicated diabetes in cases of long duration is consistent with the conception of regeneration of the Islands of Langerhans. The first two years of the disease constitute the danger zone, during which period special effort should be made to protect the patient against coma. The disturbed carbohydrate metabolism giving rise to abnormal fat or protein metabolites may be a contributing cause of the high incidence of vascular disease in diabetic patients.—J. C. D.

Use of insulin in eclampsia. Stander (H. J.) & Duncan (E. E.), Am. J. Obst. & Gyn. (St. Louis), 1925, **10**, 823-825; Abst., J. Am. M. Ass., **86**, 650.

The treatment of eclampsia employed by Stander and Duncan is as follows: As soon as the patient is admitted the modified Stroganoff treatment is started; a specimen of blood is obtained and a chemical analysis made immediately. The sugar and carbon

dioxide values are carefully voted, and should these show an undue rise in the blood sugar and a decrease in the carbon dioxide combining power, from 15 to 25 units of insulin is administered. Usually a protective dose of glucose, about 2 gm. per unit of insulin, is also given. With a marked hyperglycemia, it is, perhaps, not necessary to give glucose with the insulin, but in such cases it is advisable to have orange juice available should the patient develop hypoglycemia. A drop in the blood sugar level and a rise in the carbon dioxide combining power, as well as a change from coma to consciousness, usually follow the administration of insulin. The indications for the use of insulin in eclampsia are coma or semiconsciousness following a convulsion, together with a carbon dioxide combining power of 30 or below and an elevated blood sugar. The dosage of insulin is gauged by the degree of hyperglycemia and the weight of the patient.

The use of insulin in surgery and obstetrics. Starr (F. N. G.), & Fletcher (A. G.), Surg. Gynec. & Obst. (Chicago), 1926, **42**, 194-195.

It is desirable to allow several days when possible for the determination of the severity of the diabetes and the required amount of insulin to maintain a normal blood sugar level while the patient is on a suitable diet. In emergency operations maximum amounts of insulin should be administered during the time that may be available before operation in order to reduce the blood sugar level. Thus liability to postoperative complications is reduced, especially with surgical infections such as with diabetic carbuncle, when reduction of blood sugar lessens danger of postoperative pyaemia or multiple abscess. Under insulin administration it is possible to prescribe any diet which may be considered necessary to strengthen the debilitated patient, especially in preparing for operation in chronic cardiovascular disease. Postoperatively, small doses of insulin, controlled by blood sugar determinations where possible, should be given as soon as food is taken. If marked ketosis occurs, with marked dehydration, it may be necessary to administer glucose and fluid intravenously (500 cc. of 5 per cent solution as often as required). In event of infection of severe toxemia relatively more insulin may be required. Similar considerations apply to the pregnant diabetic. Insulin does not appear to be called for in pernicious vomiting of pregnancy.—A. T. C.

Necropsy findings in diabetes. Wilder (R. M.), South. M. J. (Birmingham), 1926, **19**, 241-248.

The author summarizes his results as follows:

An analysis is presented of the pathologic conditions found in a group of 81 fatal cases of diabetes. Diabetes was solely and directly responsible for death in 10 cases, death in the remainder

being due to degenerative complications or to the consequences of operations. Necropsy was performed in 58 cases. Gallstones were found in 16 of the 58 cases at necropsy. Pancreatic stones were found in 3 cases. Sclerosis of the kidneys occurred in 14 instances, and chronic diffuse nephritis in 4. Arteriosclerosis of considerable degree occurred in nearly all cases when the age of the patient exceeded 40 years. Gangrene accounted for 14 of the 81 deaths and was associated with a high degree of coronary sclerosis and myocardial damage in 75% of cases in which the heart was examined at necropsy. A very high incidence of advanced coronary sclerosis was encountered in the series as a whole (17 cases among 58), associated usually with marked fibrosis of the myocardium. In 4 cases exophthalmic goiter and diabetes were combined. In two of them the pancreas revealed little or no anatomic abnormality. Hydropic degeneration was not recognized, but marked fatty changes in the islands occurred in 11 cases. In several cases, representing the most severe and intensive instances of diabetes in the series, the pancreatic lesions were trivial. On the other hand, severe pancreatic lesions were frequently found in cases of relatively mild diabetes, in which death was due to degenerative complications. A parallelism between the degree of parenchymatous changes and the intensity of the clinical symptoms of diabetes does not exist. The explanation of the cause of diabetes must involve considerations such as heredity of predisposition and ability of cells other than those of the pancreas to elaborate insulin.—J. C. D.

Function of the parathyroids (Experimentelle Untersuchungen über die Funktion der Epithelkorperchen). Ogawa (S.), Arch. f. exp. Path. u. Pharmakol. (Leipz.), 1925, **109**, 83-107.

The author, using rats and rabbits, undertook to demonstrate the influence of parathyroid and of thyroid function upon the healing of fractures and also upon the calcium deposition within bones. The work attempted was extensive but the number of animals used was not sufficient for all the experiments attempted. He finds that parathyroid insufficiency delays callous formation and calcification, and that these processes are accelerated following parathyroid feedings. Thyroid extirpation caused no noteworthy alterations in callous formation. Thyroid feedings, however, inhibited callous formation. Some increase in weight was observed which was due to a greater water content. Thyroidectomy and subsequent thyroid feedings produced an increase in the water content but a decrease in the ash and calcium percentage of the callous as compared with those observed following thyroidectomy alone. Thyroparathyroidectomy caused a decrease in the weight of the callous, a rise in the water content of the callous, and decrease in the ash and calcium content. Parathyroidectomy followed by acute fetal tetany in rats caused inconstant results as regards the constituents of

bone. There was a decrease in the calcium content which seemed to be related to the acuteness and severity of tetany. The feeding of parathyroid substance caused an increase in the calcium content of bone. Thyroidectomy alone caused a slight drop in the water and the ash content of bone. These values were increased following thyroid feedings. The author finds nothing significant of influence of thyroid function upon the healing of fractures. The retardation observed by others following thyroidectomy is due to parathyroid tissue being removed along with the thyroid. He believes there is an antagonism between the thyroid and parathyroids as far as influencing bone healing is concerned.—S. Shapiro.

Function of the parathyroids. II. As a heat regulating organ. Ogawa (S.), Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1925 **109**, 300-317; Abst., Chem. Abst., **20**, 442.

Extirpation of both the thyroid and parathyroid glands results in a disturbance to the heat-regulating mechanism. In rats and in rabbits the removal of the parathyroids alone intereferes with heat control. The injection of parathyroid preparations somewhat compensates for the loss in regulatory function in animals deprived of both thyroid and parathyroid glands, while the injection of thyroid preparation fails to prevent the disturbance. In animals deprived of the parathyroids, as in those lacking both the thyroids and parathyroids, warming is followed by the onset of intense convulsive attacks, but in rats lacking thyroid substance these attacks do not occur if parathyroid tissue remains intact. Thus, the hormone of the parathyroid, but not that of the thyroid, is involved in heat regulation.

The prevention and cure of tetany by oral administration of magnesium lactate. Wenner (W. F.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1926, **23**, 432-434.

The work was done on parathyroidectomized dogs. Magnesium lactate was given by stomach tube. The magnesium in most cases protects the animal but acts by sparing the calcium and has little direct action in preventing tetany. If the serum calcium falls below 7 mg. per 100 cc. and tetany develops, the calcium defect must be repaired by giving milk or calcium lactate. Magnesium lactate has no effect on the animal until this is done. After a period of forty days' treatment with magnesium lactate most of the animals cease to be in danger of tetany and can eat large amounts of meat without ill effects.—J. C. D.

The internal secretion of the pineal gland of the rat. (Zur Frage der inneren Sekretion der Zirbeldrüse bei der Ratte). Hofmann (E.), Arch. f. d. ges. Physiol. (Berl.), 1925, **209**, 685-692.

Using Kolmer's method the pineal was completely cauterized

in 5 of 27 young rats, without other marked destructive changes. There followed no noticeable effect on body weight, growth or body fat, and there were no definite appearances of earlier sexual maturity, though the seminal vesicles were enlarged. Heat regulation was not disturbed. Thymus, spleen, testes, pancreas, liver, and kidneys showed no change in relative size.—A. T. C.

Infantile thymic hyperplasia. Macneill (N. M.), Arch. Ped. (N. Y.), 1925, **42**, 821-824.

Five cases are reported. All of the children were brought to the clinic because of some respiratory difficulty. Following roentgenological treatment there was a marked abatement of the respiratory difficulty. They all showed some thymic hyperplasia before treatment was instituted.—M. B. G.

The effect of thyroxin on the respiratory and nitrogenous metabolism of normal and myxedematous subjects. Boothby (W. M.), Sandiford (I.), Sandiford (K.) & Slosse (J.), Ergebn. d. Physiol. (Wiesb.), 1925, **24**, 728-756; Abst., Chem. Abst., **20**, 447.

Following the administration of thyroid or thyroxin to two myxedematous and one normal subject there is a temporary rise in N excretion which indicates an increased catabolism of stored protein but which is without effect on true endogenous protein metabolism. With the subject originally in N equilibrium and kept on a constant protein intake, there is an immediate large increase in N elimination with a correspondingly large negative N balance during the period when the heat production is being elevated on account of the administration of thyroxin; however, after the heat production has reached its maximum and is maintained there by small doses of thyroxin, there is a gradual decrease in N output for two to four weeks, until it has reached its former value. Creatinine and uric acid elimination are unchanged following thyroxin although there is a slight excretion of creatine during the period of ingestion when compared with the N loss indicates the breakdown of an albuminous fluid of about 2% N, which is probably responsible for the edema of myxedema. There were no changes in the non-protein N or other N partition products in the blood of the normal after thyroxin; in the myxedematous patients an increased blood urea resulted. The decay curves showing the effect of thyroxin on the basal metabolism with their mathematical formulas are given.

Bacteriology of the thyroid gland in goiter. Cantero (A.), Surg. Gynec. & Obst. (Chicago), 1926, **42**, 61-63.

Streptococcal flora are predominant. This seems of some significance since enlargement of the thyroid and true thyroiditis are

so commonly noted in diseases due to streptococci or associated with local streptococcal infections.—A. T. C.

Effect of compound solution of iodin and rest in the surgery of exophthalmic goiter. Clute (H. M.), J. Am. M. Ass. (Chicago), 1926, **86**, 105-109.

In over 200 cases of exophthalmic goiter a compound solution of iodin was given in preparation for thyroidectomy. Sixty-nine of those in whom complete data were at hand were carefully studied. Results of the iodin treatment were analyzed from the alterations in basal metabolic rate and clinical observations. Severely toxic patients dangerously ill are given large doses of Lugol's solution without preliminary metabolism determinations. The drug is given by mouth or by rectum. If necessary it may be given well diluted intravenously or subpectorally. Iodine produces marked histological changes in the thyroid gland. The papillary projections with high epithelium are replaced by vesicles lined by low epithelium and filled with colloid. The degree of involution of the gland varies directly with the iodin content. The degree of hyperplasia is inversely proportionate to the iodin content. Marked involution followed iodin feeding in exophthalmic goiter in 87.9% of cases. There are certain cases, however, that show involution histologically who nevertheless are still very toxic clinically. The effect of iodin on the symptoms of exophthalmic goiter is usually marked. The nervous symptoms are especially affected. The tremor and exophthalmos often disappear. The unrest and nervousness become less. The delirium clears up. Gastro-intestinal crises usually disappear. The basal metabolism in this series averaged +77 before iodin and rest in bed. After 8 to 10 days it fell on an average 30 points. Before the use of iodin and rest only 38% of our cases could have a subtotal thyroidectomy in one stage. Since the use of iodin and rest 63.7% have been operated upon in one stage. Iodin and rest in bed have practically eliminated pole ligations from our list of operative procedures. Only 13% in this group of 69 patients were ligated before thyroidectomy. Before the use of iodin and rest 51% had preliminary ligations. Only one pole ligation was performed in our clinic in 1925. Ligation is of little value after iodin and rest in bed in reducing the basal rate. Only 7.2% of these subjects failed to show an appreciable drop in metabolism after the use of iodin and rest. The results following subtotal thyroidectomy in one operation or when divided into two hemithyroidectomies are similar. Iodin administered over long periods without thyroidectomy does not cure exophthalmic goiter. Thyroidectomy must be added to iodin and rest in bed in the treatment of exophthalmic goiter to produce a return to normal health.

— Author's Abst.

Syndromes of hypothyroidism and obsessive syndromes (Sindromi di ipotiroidismo e sindromi obsessive). Coppolla (A.), (Siena), 1925, S. Bernardino.

Coppola tries to explain the pathogenesis of these apparently paradoxical syndromes, as found in two subjects undoubtedly affected with hypothyroidism. He begins by discarding the "unstable thyroid" of Levi and Rothschild as a factor, because at autopsy in one of the subjects no thyroid was found. According to the author the syndrome of psychic incoercibility is not necessarily of hyperthyroidal origin. Given a predisposition to such symptomatology, which has been hidden by existing hypothyroidism, thyroid medication will establish the syndrome.—G. Vercellini.

Hyperthyroidism in children. Dinsmore (R. D.), Surg. Gynec. & Obst. (Chicago), 1926, **42**, 172-176.

Report of a series of cases, the subjects ranging from 5½ to 14 years. The disease is considered to be commoner among children than is usually supposed. A small percentage of cases of the disorder follows acute infection, but there is usually no tangible factor to which the disease can be attributed. The onset is abrupt and the clinical course rapid. Induced hyperthyroidism may follow the prophylactic use of iodine in a very small percentage of cases, but can usually be controlled by discontinuance of the iodine. Such hyperthyroid children are extremely susceptible to all kinds of operative procedure. Where there are other foci of infection the goiter should be removed first, the other foci of infection subsequently.—A. T. C.

The care of the handicapped goiter patient. Dinsmore (R. D.), Surg., Gynec. & Obst. (Chicago), 1926, **42**, 177-179.

Myocardial changes, hyperthyroid children, adenomata of long standing in old people, and intrathoracic goiters are considered. By the employment of absolute rest in bed with sedatives, of large quantities of fluid, of blood transfusions (especially in delirious patients) of Lugol's solution, of guarded doses of digitalis, of local anesthesia, with light gas-oxygen anesthesia or analgesia, of a multiple stage operation performed in the patient's room, the handicapped goiter patient has the advantages of manifold measures for his protection. The maximum improvement after Lugol's solution is apparently on the eighth day. It is considered advisable to delay operation for further four days, since sometimes the patients appear to be in better condition at the eighth day than is actually the case.—A. T. C.

Substernal thyroid. Felberbaum (D.) & Finesilver (B.), Am. J. M. Sc. (Phila.), 1926, **171**, 218-227.

From a review of the literature and personal study of cases, of which seven are reported, the authors conclude that substernal thyroid is more frequent than is usually believed. Any shadow in the upper mediastinum, which shows a distinct line of demarkation, and is separate from the aorta, is usually a retrosternal goiter. Fluoroscopic examination reveals the absence of expansile characteristics. The mass moves with the trachea during respiration. A visible goiter, plus signs of compression; or signs of compression, plus thyrotoxic symptoms, are indicative of a substernal goiter. Auricular fibrillation associated with indications of a mass behind the manubrium sterni points toward the existence of a substernal thyroid.—R. G. H.

A comparative study of the effect of two different preparations of iodine upon the preoperative basal metabolic rate in exophthalmic goiter. Fitzgerald (R. R.), Canad. M. Ass. J. (Montreal), 1926, **16**, 159-161.

Lugol's solution, containing 20 grains iodine to the ounce, was compared with a solution of iodine in hydriodic acid containing 100 mg. iodine per cc. Both solutions effected lowering of the basal metabolic rate in nearly all cases to the same extent and in the same time, but it was necessary to give nearly four times as much iodine in the hydriodic acid to produce the same clinical result as with Lugol's.—A. T. C.

Carbohydrate loss from the liver of hyperthyroidized rats. Evaluation of thyroid preparations (Ueber den Kohlenhydratverlust der Leber hyperthyreoidisierter Ratten. Zugleich ein Beitrag zur Frage der Wertbestimmung von Schilddrüsenpräparaten). Fukui (T.), Arch. f. d. ges. Physiol. (Berl.), 1925, **210**, 410-426.

A method of evaluation of thyroid preparations is based on the glycogen loss from the liver following thyroid feeding. Muscle glycogen is unaffected. A parallelism between iodine content and thyroid activity is not shown by this test, though some preparations with very low iodine content were found inactive. Injection of sodium iodide did not produce the effect. Iodalbacid, given in relatively much greater doses, produced a marked lowering of liver glycogen.—A. T. C.

Total thyroidectomy in thyrotoxicosis of the exophthalmic type. A preliminary report. Gilman (P. K.) & Kay (W. E.), Am. J. M. Sc. (Phila.), 1926, **171**, 239-245.

In view of frequently encountered disappointing final results and on the principle that diseased tissue should be removed, the authors performed complete thyroidectomy in ten cases. The evidence so far accrued indicates that in selected cases, at least, a total thyroidectomy is indicated. For all cases requiring operation

a much larger amount of thyroid gland should be removed than is at present usually done, as it is believed that the entire gland is diseased and normal should be substituted. The postoperative reaction appears to be inversely proportionate to the amount of gland removed. This apparently applies likewise to the period of convalescence. It is difficult in cases of total thyroidectomy to maintain a proper thyroid balance with a thyroid preparation, if regulated from time to time by basal metabolic determinations. A number of these patients are able to determine subjectively the amount of thyroid extract they require. In seemingly hopless cases of exophthalmic goiter the results of total thyroidectomy have been most gratifying. The patients after long periods of complete invalidism have resumed their usual occupations and enjoy good health. While total thyroidectomy has been confined for the most part to those patients who were seemingly hopeless and had been invalids for long periods of time, it is felt that the procedure may be extended to embrace less severe cases. The grounds for the belief are that: (1) the entire gland is diseased; (2) the amount to be removed is indeterminate and the subsequent action of the amounts of gland remaining is likewise indeterminate.—R. G. H.

Method of palpating lobes of thyroid. Lahey (F. H.), J. Am. M. Ass. (Chicago), 1926, **86**, 813-814; Abst., A. M. A.

The method of palpating the thyroid lobes employed by the author consists first in elevating the patient's chin, thus throwing the larynx and trachea forward. Then the chin is rotated slightly toward the side on which the lobe of the thyroid is to be palpated, relaxing thus the sternomastoid on that side and permitting the examining fingers to press deeply in behind it. The original and valuable portion of the method consists in placing the ball of the thumb against the lower lateral portion of the thyroid cartilage and the upper ring or two of the trachea. The trachea is then dislocated laterally, as far as possible without causing choking. By this maneuver the lobe of the thyroid on the side opposite the pressing thumb is moved outward, together with the dislocated larynx and trachea, and is made prominent on that side of the neck. The fingers of the hand opposite that of the one whose thumb is making counterpressure now press deeply inward behind the sternomastoid and behind the thyroid lobe, and the thumb of that hand is brought over the anterior surface of the gland anterior to the sternomastoid. The dislocated lobe may then be palpated between the two. If any difficulty is experienced in distinguishing that the structure grasped between the fingers and the thumb actually is thyroid, the patient may be requested to swallow, when the lobe will be felt to fall and rise between the thumb and fingers of the examining hand, giving information not only as to its thickness and consistency, but also as to its upper and lower limits. The fingers then being oriented as to

the location of the lobe, greater dislocation of the thyroid cartilage and trachea by increased counterpressure may be made and, if necessary, a deeper grasp taken with the fingers and thumb on the dislocated lobe. Lahey says that the advantages of this method of palpating the thyroid lobe are most marked when the thyroid enlargement is slight or doubtful, as particularly occurs in cases of doubtful exophthalmic goiter. It is of value also when one wishes to determine whether or not local enlargements of the thyroid are adenomatous or malignant in character. In making lateral pressure with the thumb, care should be taken to see that the pressing thumb is placed largely against the thyroid cartilage, for if pressure is made largely on the trachea, as one may demonstrate on himself, choking results. In feeling for the back of the dislocated gland, the fingers must be pressed in deeply well behind the sternomastoid and behind the great vessels of the neck.

The action of thyroxin on the human organism. I. The influence of respiratory metabolism by thyroxin. Löhr (H.) & Freydank (W.), Ztschr. f. d. ges. exper. Med. (Berl.), **46**, 429-442; Abst. Chem. Absts., **20**, 780.

Synthetic thyroxin (Squibb), on intravenous or intramuscular injection, greatly increases oxygen metabolism. The body temperature may or may not be raised, but the increased oxidation bears no relation to changes of body temperature. There is no effect on blood pressure or activity of the heart. In myxedematous patients thyroxin is especially effective and increases oxidation with a rapidity not seen after the use of any thyroid preparation. Small doses can bring oxygen metabolism to normal, with an improvement on the symptoms of myxedema.

Anemia in hypothyroidism. Mackenzie (G. M.), J. Am. M. Ass. (Chicago), 1926, **86**, 462-464.

Three cases are reported in some detail and 14 summarized as to blood findings. Two of the three patients with hypothyroidism in whom anemia was the most conspicuous clinical fact, had no or very slight characteristics of myxedema, such as increase in weight, puffiness of the face and thickening of the skin, mental impairment, alteration in quality and quantity of hair and constipation. The most conspicuous symptom was weakness; sensitiveness to cold, decreased perspiration, paresthesia of the extremities, palpitation and dyspnea on slight exertion were also noted. The pallor of these patients may be characterized by a distinctly yellow tinge, particularly noticeable about the eyes and malar regions. One patient showed an absence of free hydrochloric acid in the gastric contents. The blood picture suggested primary anemia, but alteration in the size and form of the red cells was slight or entirely lacking in the patients observed, and there was no increase in the urobilin excre-

tion. The basal metabolic rate before treatment was between —18 and —44. Treatment with thyroid gland was followed in one case by a prompt and complete recovery and in two others by marked improvement. From these three cases and from those reported by Warfield and Greene, it is clear that thyroid deficiency occasionally causes severe anemia resembling either chlorosis or primary anemia, without proclaiming itself by the usual signs and symptoms of myxedema.—R. G. H.

Hyperthyroid experiments in dogs. I. The physiological evaluation of thyroid preparations (Hyperthyreoidisationsversuche an Hunden. I. Zugleich ein Beitrag zur Frage der physiologischen Auswertung von Schilddrüsenpräparaten). Mark (R. E.), Arch. f. d. ges. Physiol. (Berl.), 1925, **209**, 437-464.

Normal adult dogs were fed a nitrogen-free diet along with various thyroid preparations, and as measures of activity the increase in nitrogen excretion, degree of diuresis, pulse frequency, and loss of weight, were used. Iodothyrin, compared on equal iodine content, is more active than fat-free thyroid preparations.—A. T. C.

Hyperthyroid experiments on dogs. II. Action of thyroid preparations on the growing organism (Hyperthyreoidisationsversuche an Hunden. II. Wirkung von Schilddrüsenpräparaten auf den wachsenden Organismus). Mark (R. E.), Arch. f. d. ges. Physiol, (Berl.), 1925, **209**, 693-704.

Young dogs up to the age of about 16 weeks do not react to large amounts of thyroid preparations given by mouth, whether tested by protein decomposition, pulse frequency, diuresis, or loss of weight. Such a result parallels the fact that children to a certain stage react much less to thyroid than adults. The creatine excretion in young dogs is not influenced by large amounts of thyroid.

—A. T. C.

Specific dynamic action of nutrient substances. II. Action of carbohydrates and of fats and operation of the active principle of the thyroid (Ueber die spezifisch-dynamische Wirkung der Nahrungsstoffe. II. Die spezifisch-dynamische Wirkung der Kohlhydrate und der Fette. Zuzlich ein Beitrag zur Frage der Wirkungsweise der Schilddruesenstoffe). Miyazaki (K.) & Abelin (J.), Biochem. Ztschr. (Berl.), 1924, **149**, 109-135.

Using rats, the authors have determined the influence on the respiratory metabolism of feeding with sucrose, glucose, levulose, and "levoglucosan" for carbohydrates and butter, lard, cocoa butter and olive oil for fats. Simple feeding experiments are contrasted with those in which thyroid administration supplemented the specific food stuff. Both respiratory quotients and energy production were measured. Very complete protocols of the individual experiments

are presented in tabular form. The principal conclusions are: Similar to the results with protein, thyroid feeding increases to a marked degree the specific dynamic action of cane and grape sugar. Levulose alone does not affect the respiratory quotient, but thyroid feeding produces a large increase. The author draws a certain parallel with diabetics who show a normal sugar curve with levulose, while normal individuals show little if any hyperglycaemia with levulose test meals. The administration of insulin to a diabetic produces a normal curve, while the joint administration of levulose with thyroid extract gave similar results in the present studies. (Abstracter's Note.—As the shape of any sugar curve is determined solely by the relationship of the dose of sugar to the individual's tolerance, the patent explanation of these phenomena is: In the diabetic with insulin the test meal is a less massive supertolerance dose and hence conforms more nearly to the normal; while with the thyroid feeding the tolerance is lowered; the test meal becomes relatively larger in supertolerance and thus the ordinary flat curve of levulose tends toward the pointed curve of heavy supertolerance dosage.) Levulocosan with or without thyroid does not change the respiratory quotient. Gland administration, however, does increase the specific dynamic action. Animal and vegetable fats alone are without influence on the specific dynamic action. With thyroid feeding they show a 20% increase. On fat-rich diets thyroid feeding produces a less significant increase than with other dietaries. A mixture of phosphate and cane sugar increases the action of the thyroid material. The authors conclude that so-called specific dynamic action depends more on condition and reaction capacity of the organism than upon the food stuff. The differences observed between carbohydrate, fat and protein tend to disappear under the stimulus of thyroid feeding. They deduce that the thyroid influences chiefly the anabolic phase and that the equilibrium existing between syntheses and energy production are disturbed by thyroid excess, the storage phase becoming less and the energy production phase greater.—A. W. R.

The relationship of endemic goiter to certain potential foci of infection. Olesen (R.) & Taylor (N. E.), Public Health Reports (Washington), 1926, **41**, 557-571.

Examinations were made of the teeth and tonsils of 1,341 white boys and 1,576 white girls in eight schools in Cincinnati for the purpose of determining whether there was a relationship between potential foci of infection and thyroid enlargement. Records were kept of slight and marked thyroid enlargements as well as of slight and marked decay of teeth. In addition, there were recorded the number of apparently normal tonsils, the absence of tonsils through operation, hypertrophy, and cryptic degeneration. Slight thyroid enlargements prevailed to the extent of 37.2% among the boys and

50.4% among the girls. Both moderate and marked enlargements were approximately seven times more prevalent among the girls than among the boys. In the group studied, slight and marked dental decay is no more characteristically associated with thyroid enlargement than with normal thyroid status. Furthermore, the degree of thyroid enlargement appears not to be dependent upon the amount of dental decay. Normal tonsils were found more frequently among both boys and girls with thyroid enlargement than among those with normal thyroids. Approximately one-third of the children examined had had their tonsils removed by operation. A slightly greater percentage of thyroid-normal children had had their tonsils removed than those in whom the thyroid was enlarged at the time of examination. While differences may be noted in the several age groups as regards absence of tonsils, removal often being associated with a higher percentage of thyroid-normal individuals, the evidence is suggestive rather than striking. Enlargement of the tonsils was found more frequently among boys and girls without thyroid enlargement. While some of the evidence concerning hypertrophy of the tonsils in the several age groups is suggestive, the data are too uneven in trend to be convincing. There was no consistent evidence of correlation between cryptic tonsils and thyroid status. Marked thyroid enlargements among the girls are not associated with enlarged or cryptic tonsils as often as are slight thyroid enlargement. The size of the thyroid enlargement is probably independent of tonsillar or dental conditions. Based upon the material gathered during the present investigation, it is believed that there is no definite relation between thyroid status and potential foci of infection presumably located in decayed teeth and enlarged or cryptic tonsils.

The number of children included in the present survey was small and the observations were subject to manifest limitations. Before the relationship between thyroid enlargement and potential foci of infection in the teeth and tonsils can be regarded as definitely determined, it is desirable that additional studies be made in other sections of the country on a more comprehensive scale and possibly with different methods. Nevertheless, it is felt that in so far as the present study is concerned, such a relationship is non-existent.

The vital capacity in hyperthyroidism. Rabinowitch (I. M.), Boston M. & S. J., 1926, **194**, 199-201.

Twenty-two hundred observations were studied statistically. The vital capacity is reduced in hyperthyroidism. The increase in respiratory rate found in such cases is an effort of the body to maintain a normal oxygen intake and carbon dioxide output in the face of the increased metabolic rate and reduced vital capacity.

—J. C. D.

Prognosis in exophthalmic goiter. Read (J. M)., Am. J. M. Sc., (Phila.), 1926, **171**, 227-238.

From a personal study of 100 cases Read concludes that acute cases of exophthalmic goiter with well-defined onset offer a more favorable prognosis for recovery than those with insidious onset and symptoms existing for several years before seeking medical advice. The height of the basal metabolic rate offers only slight assistance in estimating the prognosis. Males with exophthalmic goiter seem more resistant to treatment and are more apt to become chronic sufferers than are females. Subtotal thyroidectomy nearly always produces a remission of the diseases if the patient survives the operation, but it does not constitute a cure.—R. G. H.

Bone formation in the thyroid gland. Seelig (M. G.), Surg. Gynec. & Obst. (Chicago), 1925, **41**, 794-797.

Case history of extensive calcification in the thyroid.
—A. T. C.

Aids in predicting the degree of postoperative thyroid reaction: a study based on 1,000 consecutive cases. Sise (L. F.), Surg. Gynec. & Obst. (Chicago), 1925, **41**, 57-62.

In the great majority of toxic thyroid patients under nitrous oxide-oxygen anaesthesia a postoperative reaction is indicated proportional roughly to the increase above normal in pulse rate, pulse pressure, systolic blood pressure, and respiration. With a small proportion of patients in a more advanced condition the reverse holds; this group is asthenic and apathetic, and their operative mortality high.—A. T. C.

The heart and its management in hyperthyroidism. Sturgis (C. S.), Rhode Island M. J., 1925, **8**, 141-146; Abst. Physical Therapy X-Ray Radium, **7**, 187.

In the treatment of patients with exophthalmic goiter and toxic adenomas who have, in addition severe cardiac failure, every resource known to be of value in the treatment of heart disease should be utilized. The patient should be placed in bed and every method used to procure rest. Drug therapy should be used as indicated assisting operative measures. Roentgen ray therapy is worthy of serious consideration in these cases. In a small group of patients, according to the author, this therapeutic measure has produced very satisfactory results. The best routine to follow is to give four exposures at intervals of three weeks. The patient is then observed for six weeks following the last treatment. The basal metabolism should be determined at frequent intervals to prevent the possibility of over-treatment and a resultant myxoedema. If striking improvement does not follow four roentgen ray exposures, little

more can be expected of this measure, and further treatment of this nature should be discontinued. This type of treatment is not strongly recommended, as the chances of cure are not great and the period of three months, over which the treatment is given, may be sufficient time in which additional cardiac injury may occur. How often one may hope to relieve cardiac symptoms in these patients is a very difficult question. In the young individual, even though the functional ability of the heart has been markedly impaired, the results are uniformly excellent, provided the underlying pathological condition of the thyroid gland is eliminated. In older patients, even though the cardiac failure is marked, it is possible to produce striking improvement following appropriate therapy directed toward the thyroid gland. These results are so satisfactory that there should be no hesitation in recommending a subtotal thyroidectomy or roentgen ray treatment.

Morbid anatomy and histology of pellagra. Susman (W.), Edinb., M. J., 1926, **33**, 58-64.

Two cases of pellagra carefully examined at autopsy showed, among other things, changes in the thyroid gland. The author concludes that the oldest lesion is in the thyroid and proliferation of the vesicular epithelium, increased vascularity, and intracellular granularity and a marked fibrosis indicate a disease of the thyroid.

—J. C. D.

The effect of the administration of thyroxin upon the surface tension of blood. Wilhelmj (C. M.) & Fleisher (M. S.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **23**, 79-80.

Guinea pigs fed thyroxin showed a fall in the surface tension of their blood. The average change in five days in 27 animals was a fall of 3.7 dynes, the average of the controls a fall of .15 dynes. If thyroxin is added directly to normal plasma there is no change in surface tension. These results agree with previous work in which thyroidectomized guinea pigs showed an increased surface tension in the blood plasma.—J. C. D.

The status of the heart in myxedema. Willius (F. A.) & Haines (S. F.), Am. Heart Journal (St. Louis), 1925, **1**, 3-7.

One hundred and sixty-two cases of high-grade myxedema were studied with special reference to the cardio-vascular system. It was found that no heart failure and no organic cardiovascular disease cases could be justly attributed to the myxedema. There were numerous electrocardiographic abnormalities which disappeared under thyroid medication. The data presented do not justify the establishment of a cardiac syndrome characteristic of myxedema.

—R. G. H.

Liver injury in thyrotoxicosis as evidenced by decreased functional efficiency. Youmans (J. B.) & Warfield (L. M.), Arch. Int. Med. (Chicago), 1926, **37**, 1-17.

Tests of liver function have been made in forty-four patients with thyrotoxicosis. The functional efficiency of the liver was determined by means of the phenoltetrachlorphthalein test as modified by Rosenthal and in a few instances by the levulose tolerance test, the hemoclastic crisis test of Widal, Abrami and Iancovesco, and by the determination of the concentration of the bilirubin in the blood serum. In 28 of the patients tests of the glucose tolerance also were made. Of the patients in this series 22, or 50%, showed an impairment of liver function. Of the 27 cases 21 satisfactorily tested showed a decreased glucose tolerance. No relation was found to exist between the functional efficiency of the liver as tested and the glucose tolerance, basal metabolic rate or other features of the disease except loss of weight. The impairment of liver function in thyrotoxicosis seems to be associated to some degree with loss of weight.—R. G. H.

A thyroid-adrenal interrelationship. Zwemer (R. L.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **23**, 31-32.

Cats deprived of their adrenals in two operations 7 days apart do not live for more than 3 days after the last operation. If the thyroid is removed and the parathyroids transplanted to avoid tetany, the cats live 9 days or more after complete adrenalectomy. If, however, thyroidectomized cats are fed thyroid extract and then subjected to removal of their adrenals, they survive the operation 2 days at most. The author concludes that his experiments demonstrate a functional interrelation between the thyroid and adrenal glands, in that the life of animals deprived of their adrenals can be greatly prolonged or shortened by absence or excess of the thyroid hormone.—J. C. D.